Society for Immunotherapy of Cancer (SITC)

Understanding Checkpoint Inhibitors: Approved Agents, Drugs in Development and Combination Strategies

John Powderly MD
Carolina BioOncology Institute, PLLC
Adjunct Clinical Assistant Professor Medicine Duke & UNC

Advances in Cancer Immunotherapy™ - Illinois
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Society for Immunotherapy of Cancer

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Overview

- Self tolerance “checkpoints”
  - PD1 & PDL1
    - Recent FDA approved indications
  - Case presentation
  - Correlates & Biomarkers
  - Combination Checkpoint blockade

2013 Science “Breakthrough of the Year”
2014 Special Nature Edition

Immune system is exponentially more adaptable then tumor

Vaccines Are *The* greatest success story of modern medicine by eradicating infectious diseases.

So why haven't cancer vaccines work?

Infections

Discriminate self from *non*-self (obvious)

Tumors

Discriminate self from *altered*-self (subtle)

Self Tolerance = Self Preservation

98% anti-self lymphocytes undergo apoptosis
Remaining T-cells >90% tolerizing surveillance

Our immune system balance favors self tolerance

CTLA-4 & PD1/PDL1: The Brakes on T cell Activation

T-cell receptor: Antigen-MHC

CD28: B7

IL-2

IFN

CTLA-4: B7

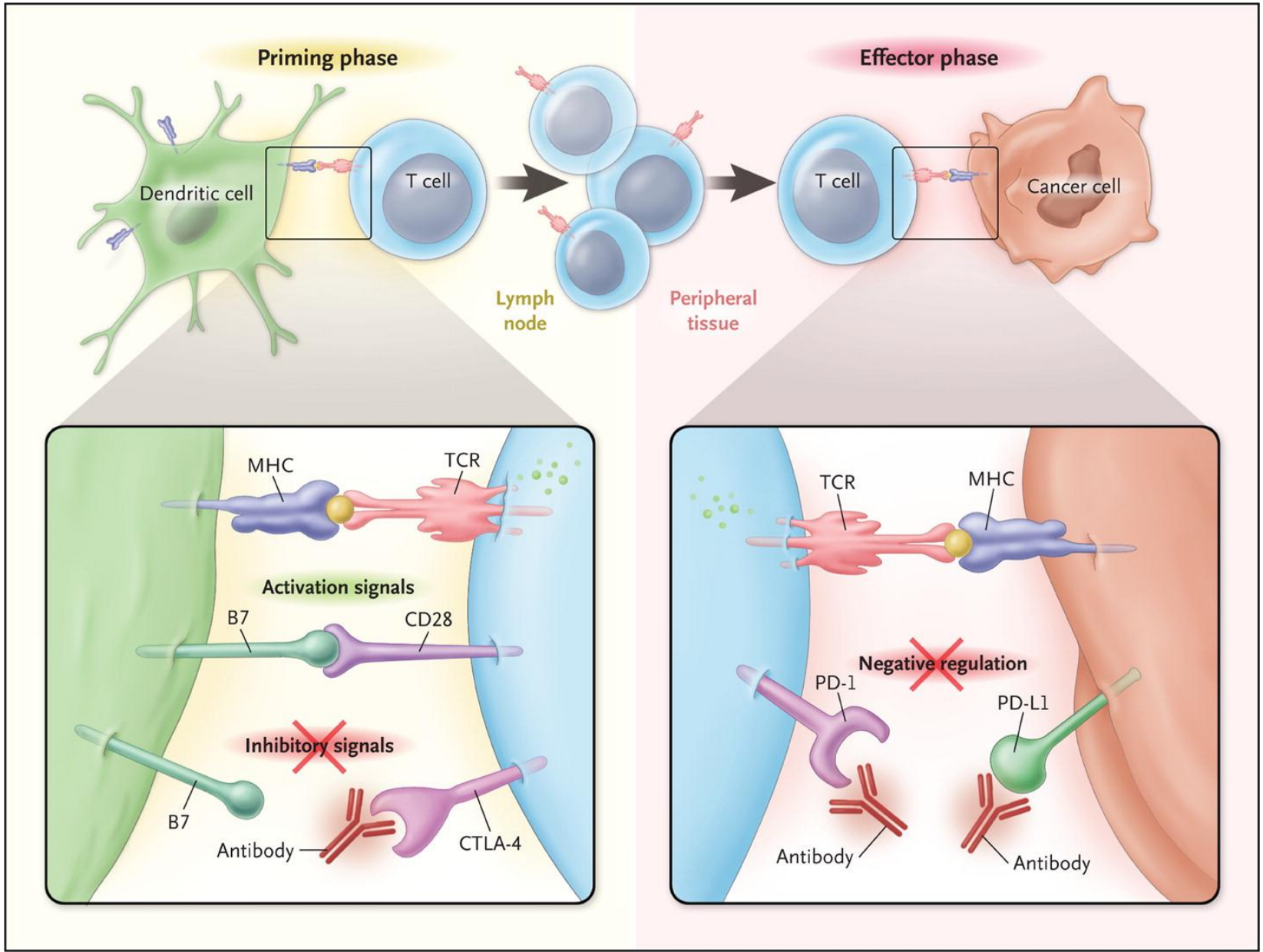
PD1: PDL1

Vaccine?

Adapted from Hodi

Tumor Immunotherapy CTLA4 vrs PD1/PDL1

Antoni Ribas, NEJM epub June 2012



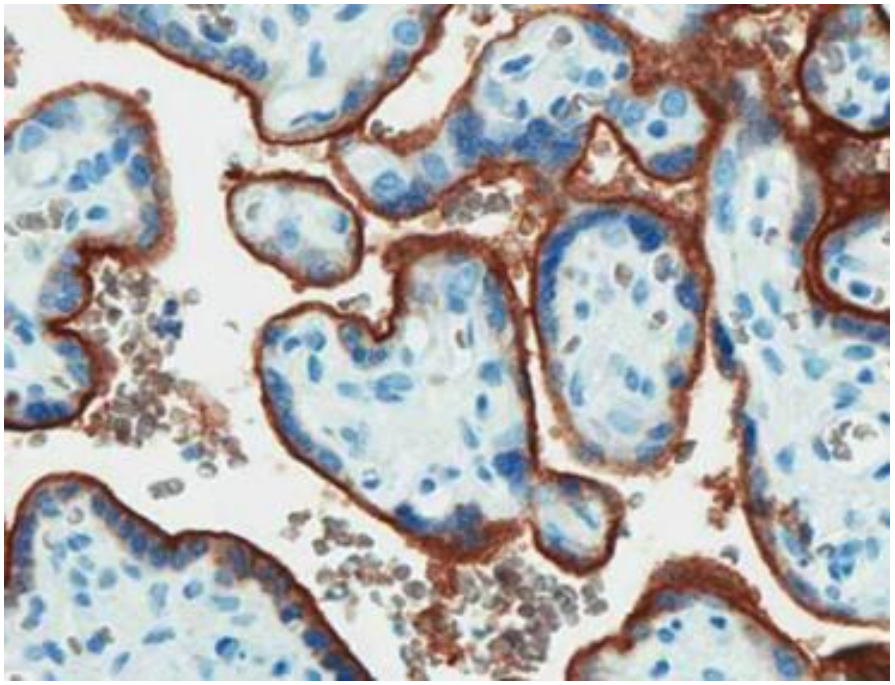
Immune Checkpoint CTLA4

- CTLA-4 “Cytotoxic T Lymphocyte Antigen 4”, receptor expressed on T cells
  - James Allison PhD discovered in 1990s,
  - Most important inhibitory receptor (tolerance) during antigen presentation in LN
  - Double gene knockout mouse model: develop lymphoproliferative disease and fulminant auto-immunity toxicity and die by 6 weeks of life.
  - Human polymorphisms are associated with familial tendency towards autoimmune diseases.
  - Ipilimumab first checkpoint inhibitor developed, anti-CTLA4 mAb

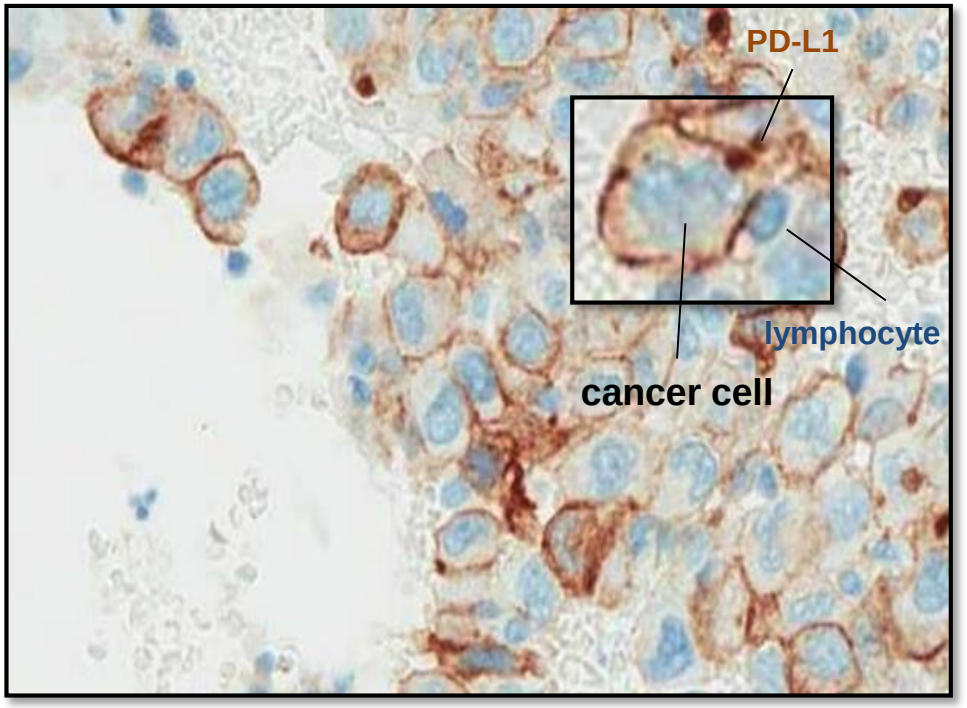
Immune Checkpoint: PD1/PDL1

- PD “Programmed Death”
  - Inhibitory effect of PD-1 is accomplished through a cell surface receptor/ligand mechanism that promotes apoptosis (programmed cell death) in antigen specific T cells, thus allowing self tolerance.
  - PD1 receptor (on lymphocytes) has two ligands: PDL1 & PDL2
  - PDL1 ligand: expressed on immune cells, and dynamically expressed in tissue (and tumors) during inflammation.
  - PD1-PDL1 axis: most important “break” (tolerance) at peripheral site of inflammation
  - Pharmacologic blockade of either PD1 or PDL1, overcomes “tolerance” and enables activated T cells to destroy tumors
  - PDL1 “shield for tumors to hide from immune cells”
  - During inflammation, interferon gamma will upregulate PDL1 expression
  - PD1 or PDL1: double gene knockout mouse model develop mild tendency towards auto-immunity with inflammatory stimuli.
  - Nivolumab & Pembrolizumab first anti-PD1 mAbs developed and FDA approved

Placenta & tumors express PDL1 to evade immune recognition



Placenta



Tumor

Checkpoint Blockade Drugs in Development

- Anti-CTLA-4
  - Ipilimumab (Fully human IgG1) FDA Approved 2011
  - Tremelimumab (Fully human IgG2) Phase III
- Anti-PD-1
  - MDX-1106, Nivolumab, (Fully human IgG4) FDA Approved Melanoma & Squamous Lung
  - CT-011 Pidilizumab (Humanized IgG1) Phase II
  - MK3475 Pembrolizumab (formerly Lambrolizumab) (Humanized IgG4) FDA Approved 2014
  - AMP-224 (B7-DC/IgG1fusion protein) Phase I-II
  - MEDI0680, AMP514 Phase I
- Anti-PD-L1
  - MDX-1105, (Fully human IgG4) Phase I
  - MPDL3280A, RG7446, Atezolizumab Phase II-III
  - MEDI4736 Phase III
  - MSB0010718C Avelumab Phase I-II

PD1 Blockade Melanoma

Nivolumab Phase I

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D. , F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

ABSTRACT

June 2012

Safety, Activity and Immune Correlates of Anti-PD1Antibody (Nivolumab) in Cancer Topalian, Hodi, Brahmer, Gettinger, Smith, McDermott, Powderly, Drake, Sznol, et al NEJM June 2012, & ASCO 2012

- Phase Ib, 296 patients solid tumors stage IV
  - Rx monotherapy mAb Q2 weeks (4 doses over a 8 week cycle) upto 12 cycles until PD or CR
  - Cumulative objective response (RECIST)
    - Melanoma 28%
    - Renal Cell Cancer 27%
    - NonSmall Cell Lung 18%
  - 65% of Responders were durable > 1 year
  - Drug related AEs 14% (fatigue, cough, fever, rash, diarrhea, nausea)
    - Drug related Grade 3-4 toxicity 11%,
    - Grade 3-4 pneumonitis 1%, including 3 deaths from pneumonitis (2 NSCL, 1 renal)
    - MTD not reached; 5% of patients stopped therapy due to AEs.
  - Among 42 archived tumors, response correlated with PDL1 tumor expression (p=0.006)

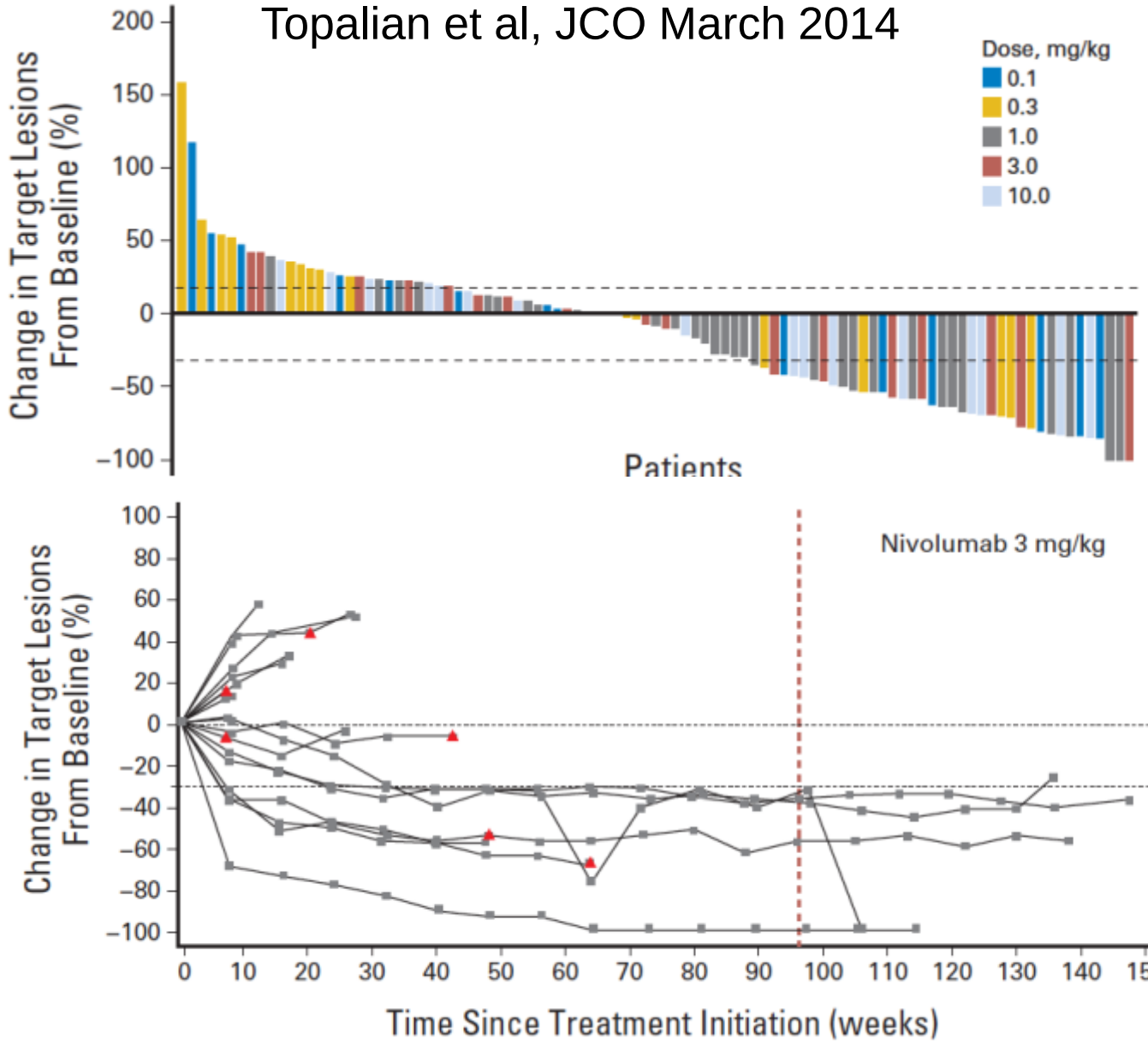
Survival, Durable Tumor Remission, and Long-Term Safety in Patients with Advanced Melanoma Receiving Nivolumab

Topalian et al, JCO March 2014

- 107 patients, phase Ib, 2-5 prior regimens
  - All dose cohorts
    - ORR 31%
    - median survival 16 months
    - 1 year OS 62%, 2 year OS 43%
  - 3mg/kg IV Q 2 weeks
    - ORR 41%
  - Toxicity: fatigue 32%, rash 23%, diarrhea 18%
    - Grade 3-4 Immune toxicity 5% (no deaths in melanoma cohort)

Survival, Durable Tumor Remission, Long-Term Safety in Advanced Melanoma Receiving Nivolumab

Topalian et al, JCO March 2014



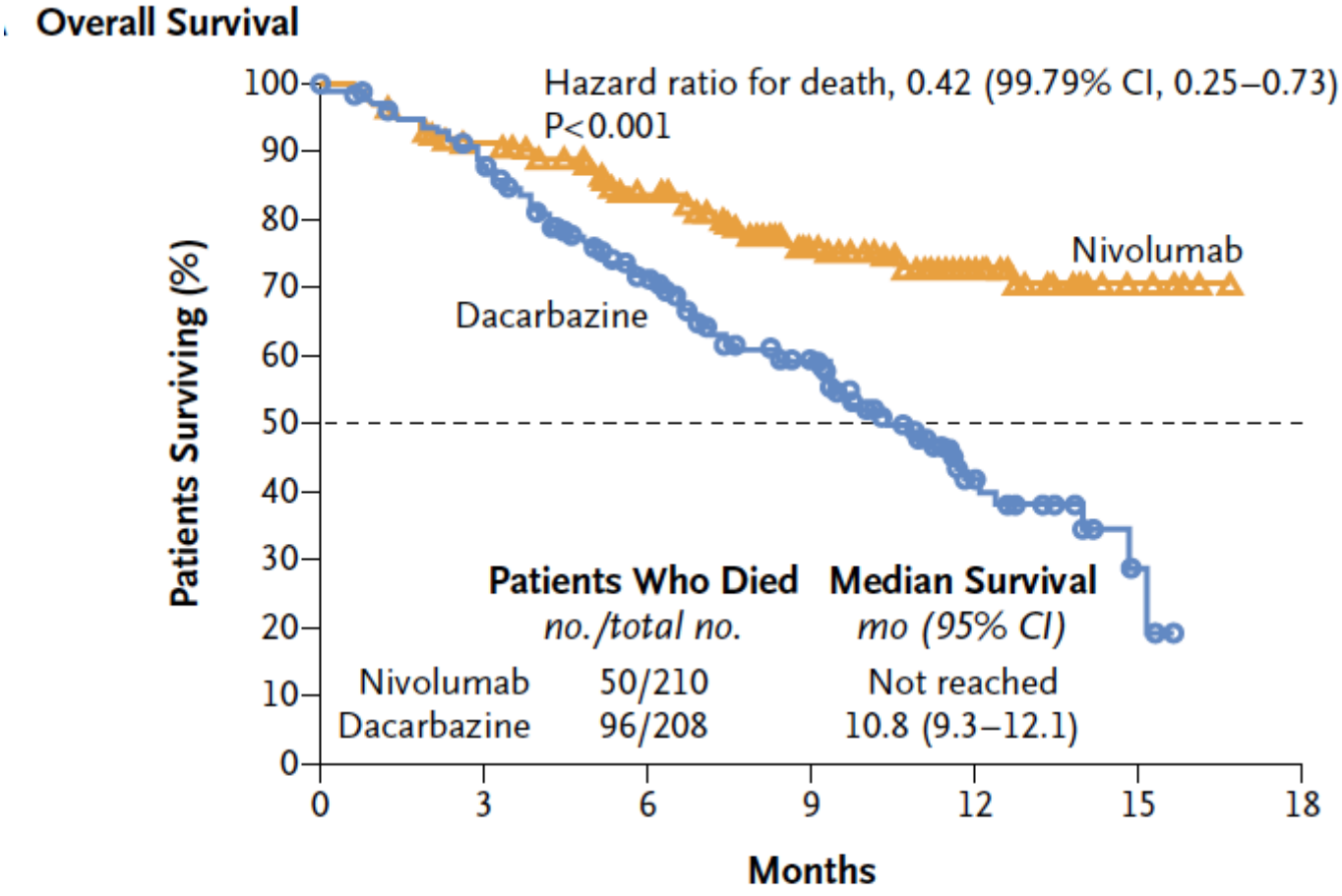
Nivo 3mg/kg Q2W vrs Chemo 2nd or 3rd line "CHECKMATE 037"

FDA Package Insert, 2015 (full data to be published)

- Randomized Phase 3 study of 370 patients
  - Must have progressed after prior IPI, and BRAF inhibitor (if BRAF mutant).
    - 18% of patients had stable treated brain mets
  - Interim analysis of initial 120 patients:
    - ORR = 32% (3.5% CR + 28.5% PR) confirmed RECIST
      - Responses seen in both BRAF mutant & wild type
      - Among responders, 87% were durable
      - 9% patients discontinued due to adverse events.
    - Immune mediated toxicity: pneumonitis 3.4%, colitis 2.2%, hepatitis 1.1%, nephritis 0.7%, thyroiditis 11%
  - FDA Approval based on interim analysis

Nivolumab Vrs DTIC Front Line Melanoma (BRAF WT)

Robert et al, NEJM Nov 2014



Pembrolizumab Phase I (Formally Lambrolizumab)

The NEW ENGLAND JOURNAL of MEDICINE 2013

ORIGINAL ARTICLE

Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma

Omid Hamid, M.D., Caroline Robert, M.D., Ph.D., Adil Daud, M.D., F. Stephen Hodi, M.D., Wen-Jen Hwu, M.D., Ph.D., Richard Kefford, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Richard W. Joseph, M.D., Jeffrey S. Weber, M.D., Ph.D., Roxana Dronca, M.D., Tara C. Gangadhar, M.D., Amita Patnaik, M.D., Hassane Zarour, M.D., Anthony M. Joshua, M.B., B.S., Ph.D., Kevin Gergich, M.A., Jeroen Elassaiss-Schaap, Ph.D., Alain Algazi, M.D., Christine Mateus, M.D., Peter Boasberg, M.D., Paul C. Tumeh, M.D., Bartosz Chmielowski, M.D., Ph.D., Scot W. Ebbinghaus, M.D., Xiaoyun Nicole Li, Ph.D., S. Peter Kang, M.D., and Antoni Ribas, M.D., Ph.D.

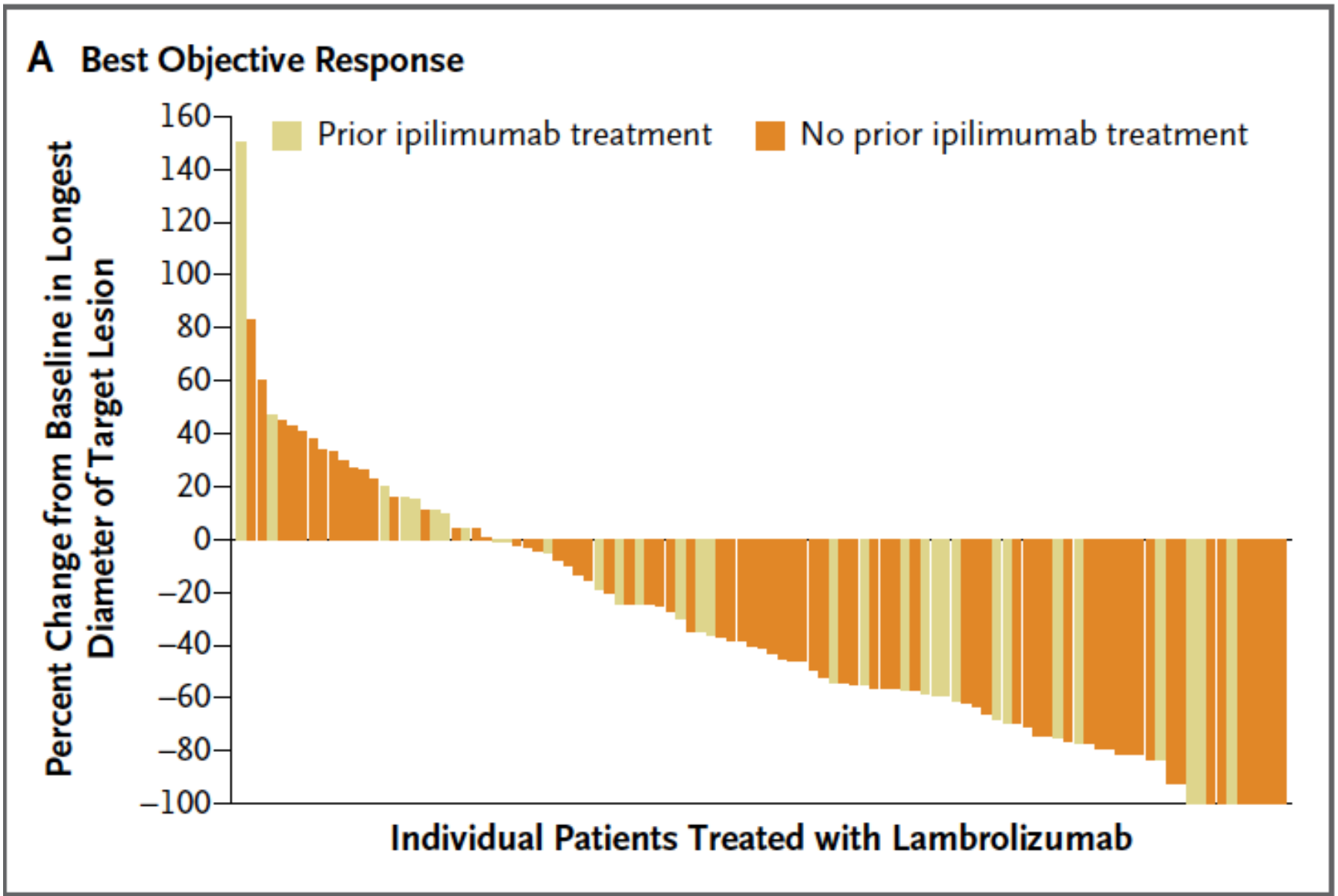
Safety and Tumor Responses with Lambrolizumab (Pembrolizumab, Anti-PD1) in Melanoma

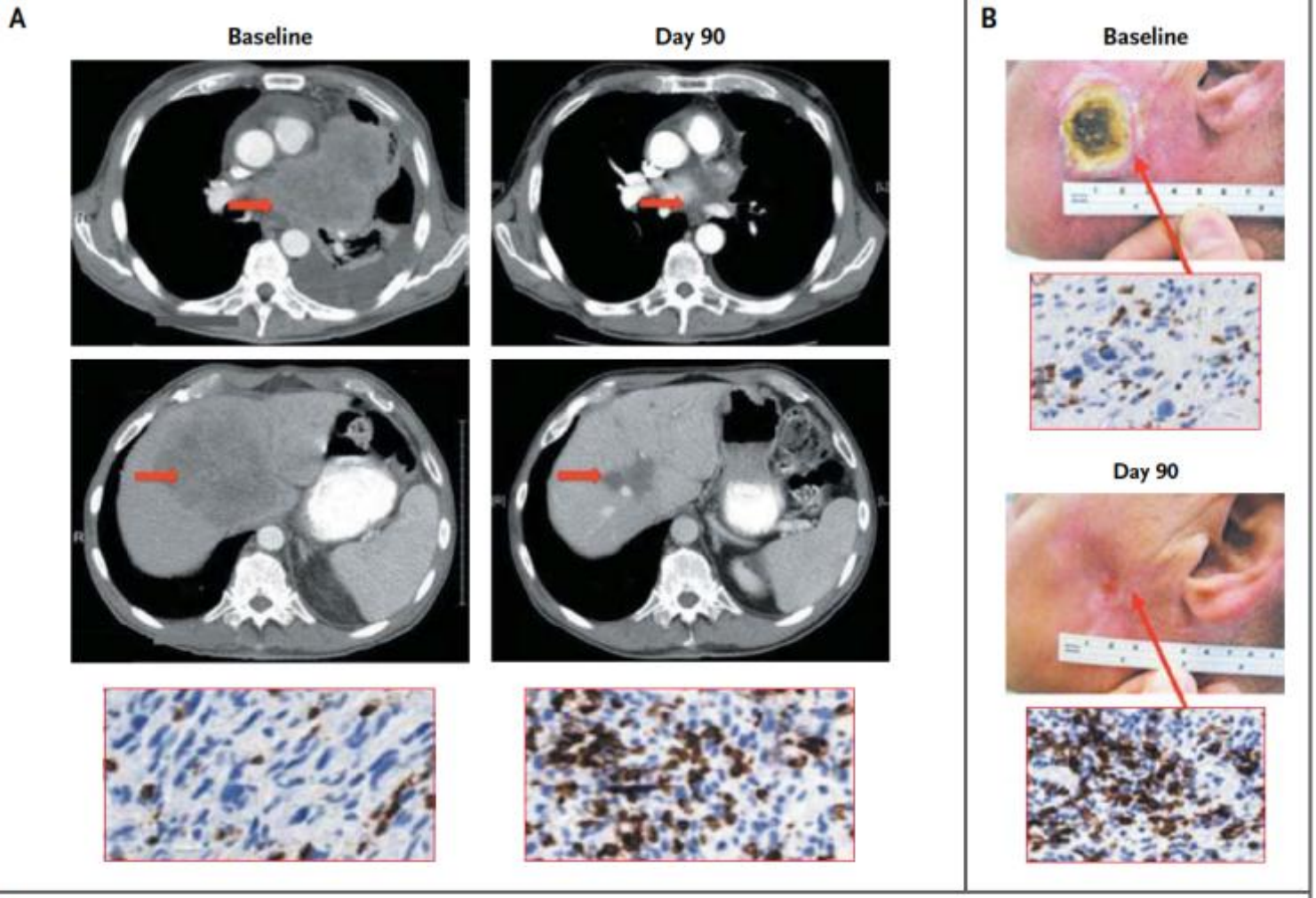
Hamid NEJM 2013

- 135 Stage IV melanoma patients (both Ipi naïve and Ipi failures)
  - 38% RECIST response rate in all dose cohorts
    - 52% RECIST highest in cohort of 10mg/kg Q2 weeks.
    - No statistical significant difference in response rate with prior Ipi exposure (but trend favored prior Ipi exposure)
    - 79% any grade drug related adverse events (fatigue, asthenia, fever, chills, myalgias, HA). 21% had rash & pruritis, 20% diarrhea, 8% hypothyroidism, 9% vitiligo.
    - 13% grade 3-4 drug related adverse events
    - Auto-immune adverse events: 4% pneumonitis

Pembrolizumab Melanoma

Hamid NEJM 2013





Pembrolizumab Responders

NEJM 2013

Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial

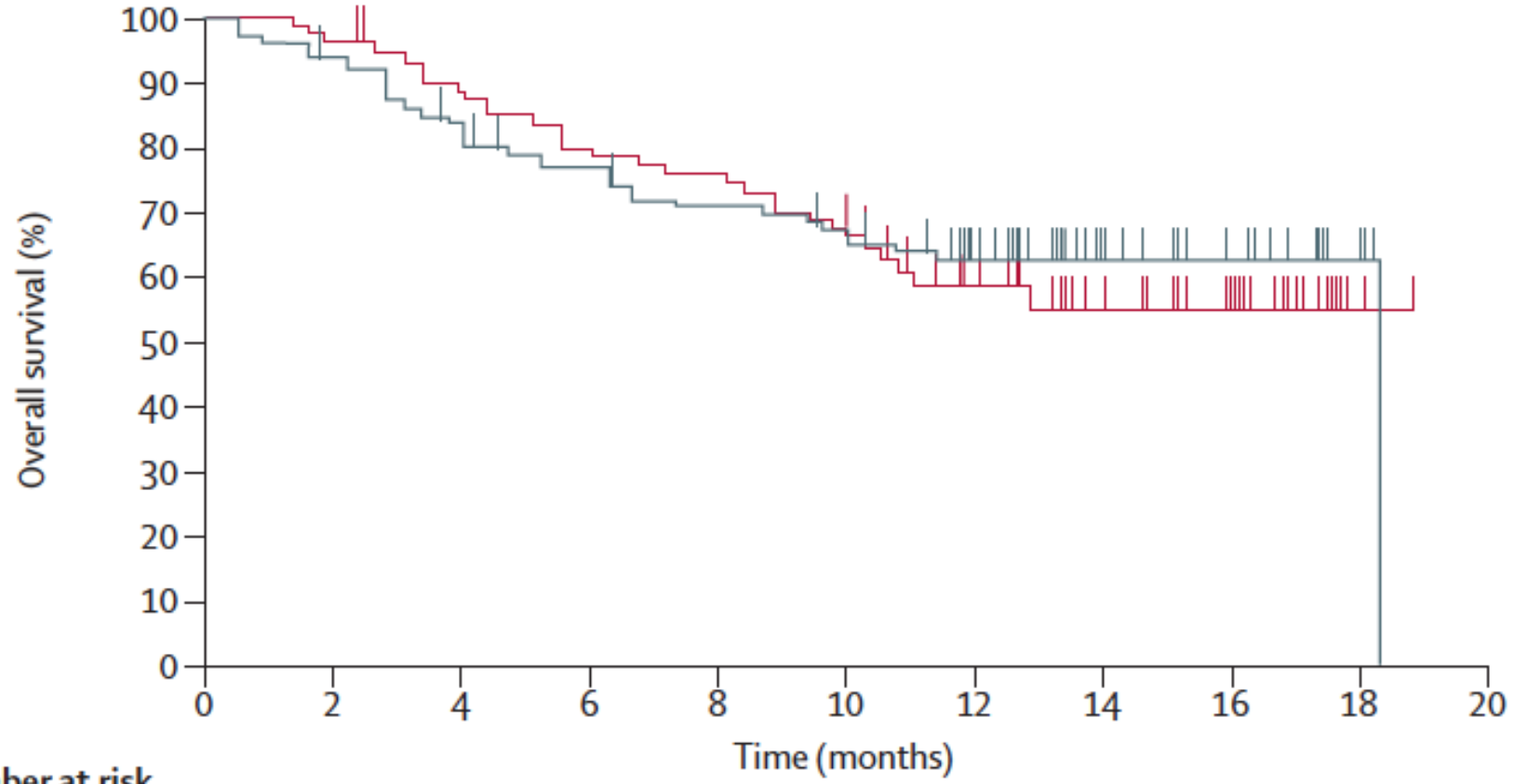
Lancet July 2014

Caroline Robert, Antoni Ribas, Jedd D Wolchok, F Stephen Hodi, Omid Hamid, Richard Kefford, Jeffrey S Weber, Anthony M Joshua, Wen-Jen Hwu, Tara C Gangadhar, Amita Patnaik, Roxana Dronca, Hassane Zarour, Richard W Joseph, Peter Boasberg, Bartosz Chmielowski, Christine Mateus, Michael A Postow, Kevin Gergich, Jeroen Elassaiss-Schaap, Xiaoyun Nicole Li, Robert Iannone, Scot W Ebbinghaus, S Peter Kang, Adil Daud

- Randomized Expansion cohort of original Phase I, additional 173 patients
- Dedicated to Ipilimumab “refractory” patients (received at least 2 doses Ipi). Excluded prior Ipi grade 3,4 toxicities. Allowed prior grade 2 toxicity, if resolved to grade 0-1, and off steroids. Stable brain mets allowed.
- 2mg/kg IV Q3 weeks vrs 10mg/kg IV Q3 weeks
- Results: ORR 26% in both doses, similar safety profiles, no drug related deaths, fatigue (33%), pruritus (26%), rash (18%). Only grade 3 drug AE was fatigue (3%).

Pembrolizumab Survival

Robert Lancet 2014



Number at risk											
Pembrolizumab 2 mg/kg	89	86	76	69	66	57	42	29	16	1	0
Pembrolizumab 10 mg/kg	84	78	65	61	55	50	37	18	12	1	0

PD1 mAb FDA Approval Melanoma

(After Ipilimumab, and BRAF inhibitor if BRAF mutant)

- Pembrolizumab FDA Approved September 2014
  - Phase IB Randomized trial 2mg/kg vrs 10mg/kg (KEYNOTE-001)
    - 2mg/kg IV over 30 minutes Q3 weeks
    - Interim analysis ORR = 24%, of which 86% durable
- Nivolumab FDA Approved December 2014
  - Phase III Randomized trial vrs Dacarbazine (CHECKMATE 037, CA209-037)
    - 3mg/kg IV over 60 minutes Q2 weeks
    - Interim analysis ORR confirmed = 32%, of which 87% durable
- Class Toxicity of PD1 mAb (all grades): pneumonitis 2-3%, colitis 2%, hepatitis 1%, nephritis 0.7%, hypo-hyperthyroidism 10%, potential embryofetal toxicity;
- Other common immune symptoms: tumor flare, fatigue, fever, pruritus, cough, diarrhea transaminitis, thyrombocytopenia, lymphopenia, hyponatremia, hyperkalemia,
- Continue “until disease progression or unacceptable toxicity”

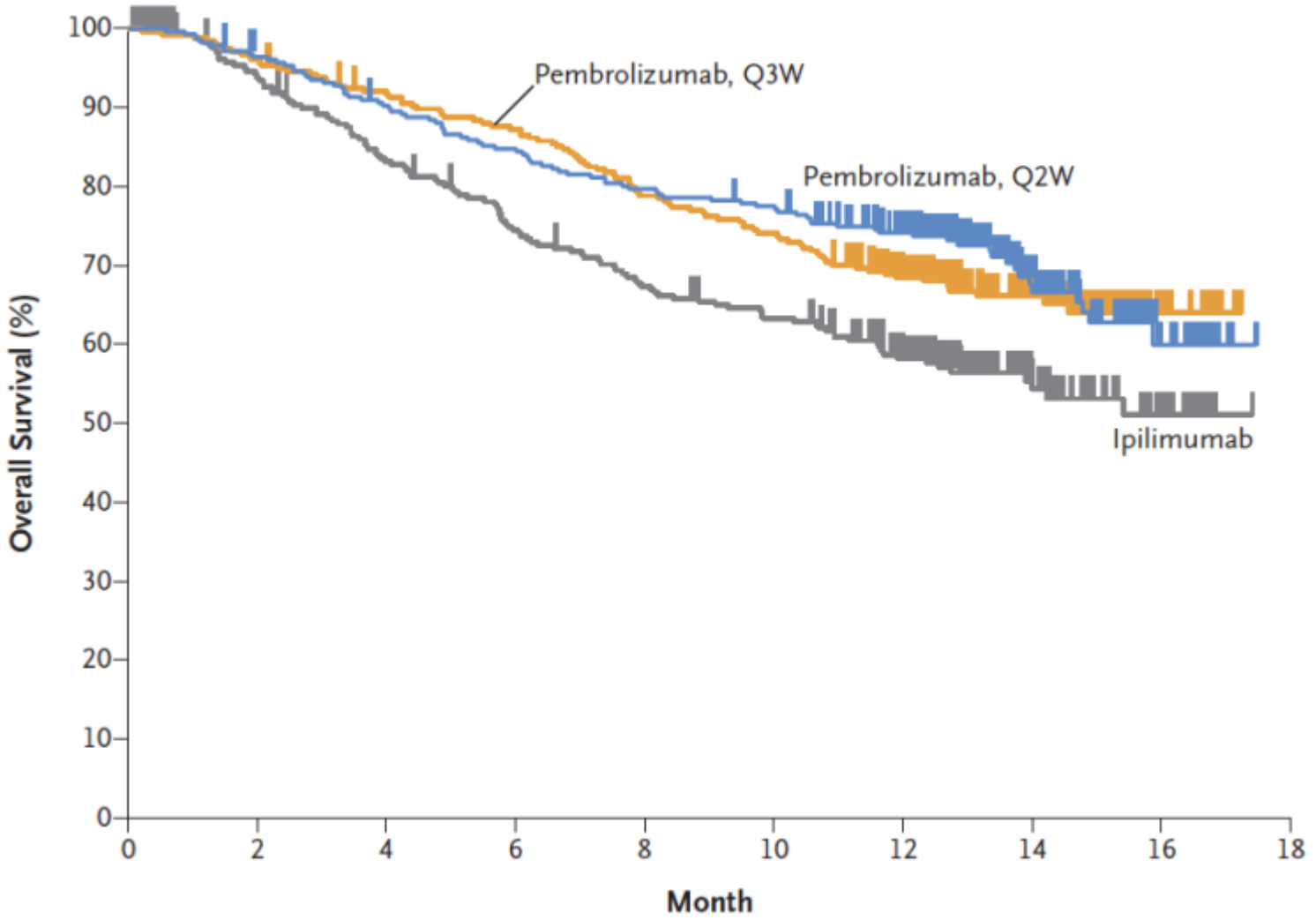
Pembro vrs Ipi in Melanoma

"Keynote 006 Study", C Robert et al, NEJM April 2015

- 824 patients, ≤ 1 prior treatment
  - Randomized 1:1:1
    - Pembro 10mg/kg Q2 weeks
    - Pembro 10mg/kg Q3 weeks
    - Ipi 3mg/kg Q3 weeks x 4 doses
  - Results:
    - Pembro ORR 33.7%, 32.9% (Q2, Q3) vrs Ipi 11.9%
    - Pembro 1 yr OS 74%, 68% (Q2, Q3) vrs Ipi 58%
  - Toxicity: Treatment related Gr 3-5 AEs
    - Pembro 13%, 10% (Q2, Q3) vrs Ipi 19.9%

Pembro vrs Ipi in Melanoma

"Keynote 006 Study", C Robert et al, NEJM April 2015



PD1 Blockade Lung Cancer

MDX-1106 001: Phase I Study of Single-Agent anti PD1 (MDX-1106, Nivolumab) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates;

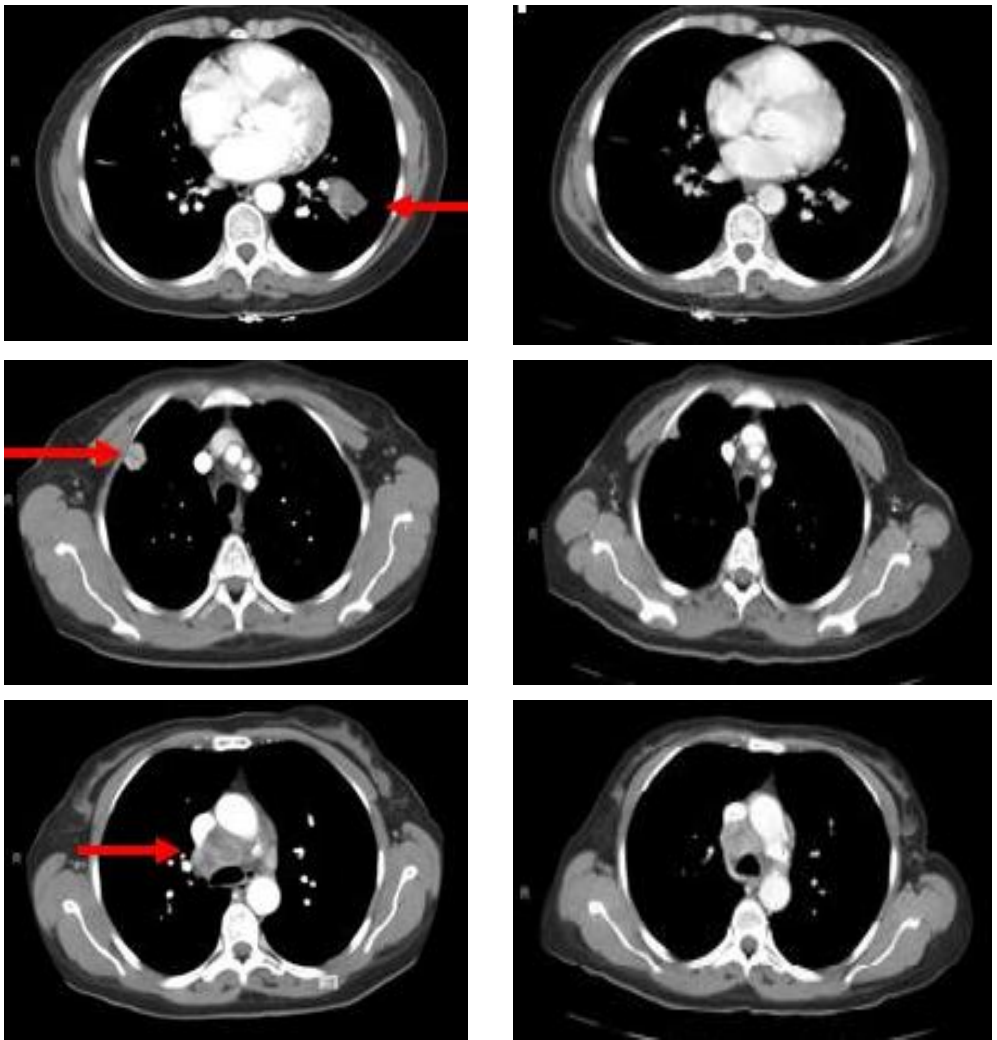
Brahmer, Drake, Wollner, Powderly, Topalian et al, JCO 2010 28:3167

61yo BF Stage IV NSCLung CA (squamous) bilateral lung metastasis, bone mets. Prior treatment carboplatin/vinorelbine/bevacizumab

May 2007, Rx single dose (first lung patient) of MDX-1106, anti-PD1mAb (1mg/kg IV)

8 week 41% RECIST partial response, but 12 week scans showed new spine mets (mixed response).

Rechallenged nivolumab, progressed



Safety, Activity and Immune Correlates of Anti-PD1 mAb (Nivolumab) in Cancer

Topalian, et al NEJM June 2012

- Among the 122 NSCLC, all failed prior chemo (94%) or TKI (34%)
  - 55% failed > 3 regimens
- NSCLung objective responders, cumulative 18% response (CR+PR)
  - By dose: 1mg/kg (6%); 3mg/kg (32%); 10mg/kg (18%)
  - By histology: 33% in squamous; 12% nonsquamous;
- NSCLung Stable disease $\geq$ 24 weeks = 7%
- NSCLung Clinical Benefit (CR+PR+SD) = 25%

Nivolumab in Patients with Previously Treated Advanced NSCLung Cancer

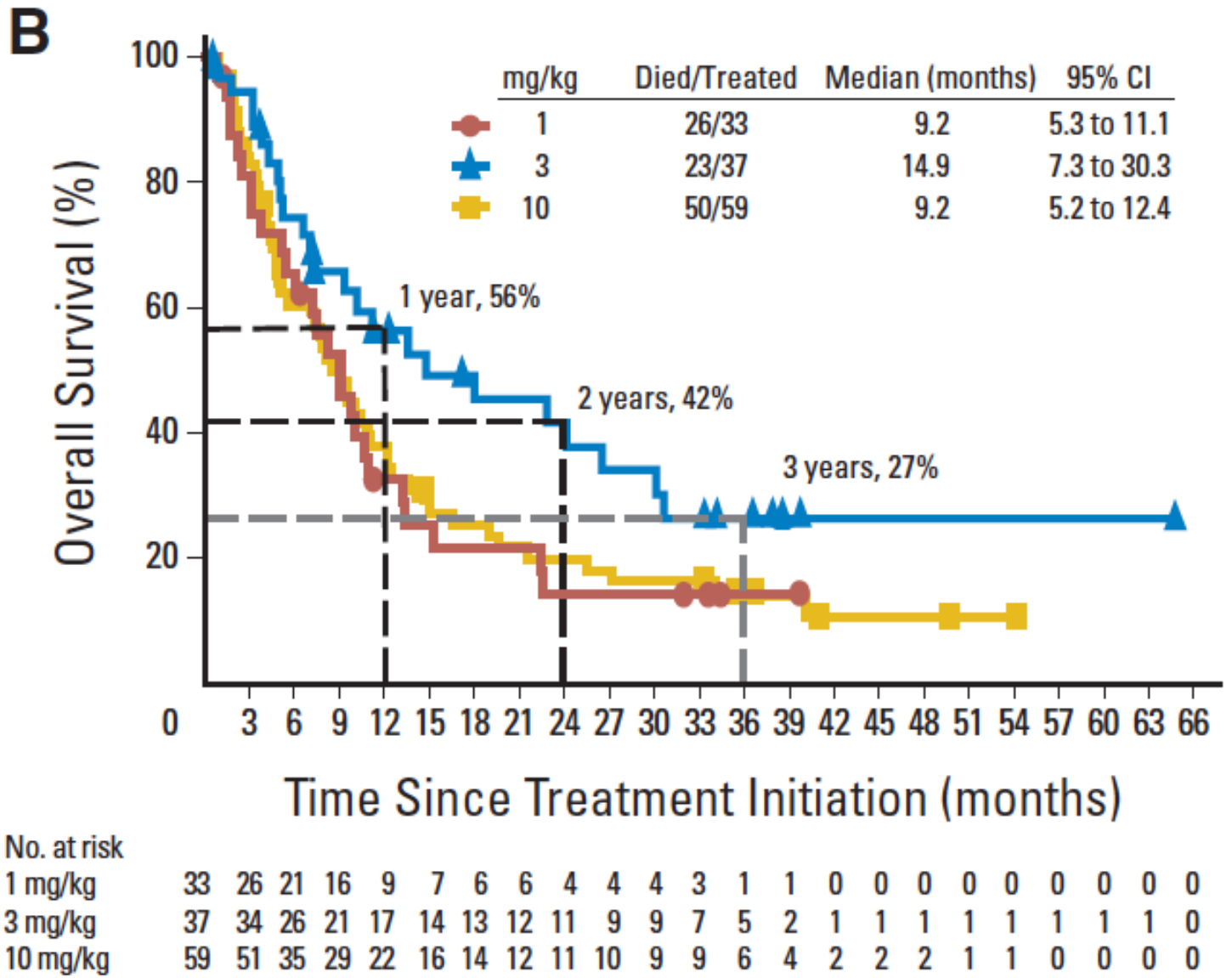
Gettinger et al, JCO April 2015

- 129 NSCLung patients
  - Phase IB, heavily pretreated population
  - 1, 3, or 10mg/kg IV Q2 weeks x 2 years

    3mg/kg chosen dose for phase III trials
- Results:
  - @ 3mg/kg OS of 1, 2, 3 year = 56%, 42%, 27%
  - @3mg/kg ORR = 24%
  - ORR higher in smokers > 5 pack year hx, 50% vrs no responses
  - PDL1 tumor expression did not correlate
  - Squamous and NonSquamous benefitted similarly
- Toxicity Grade 3-4 drug related =14%
  - Three patient deaths with pneumonitis

Nivolumab in Patients with Previously Treated Advanced NSCLung Cancer

Gettinger et al. JCO April 2015

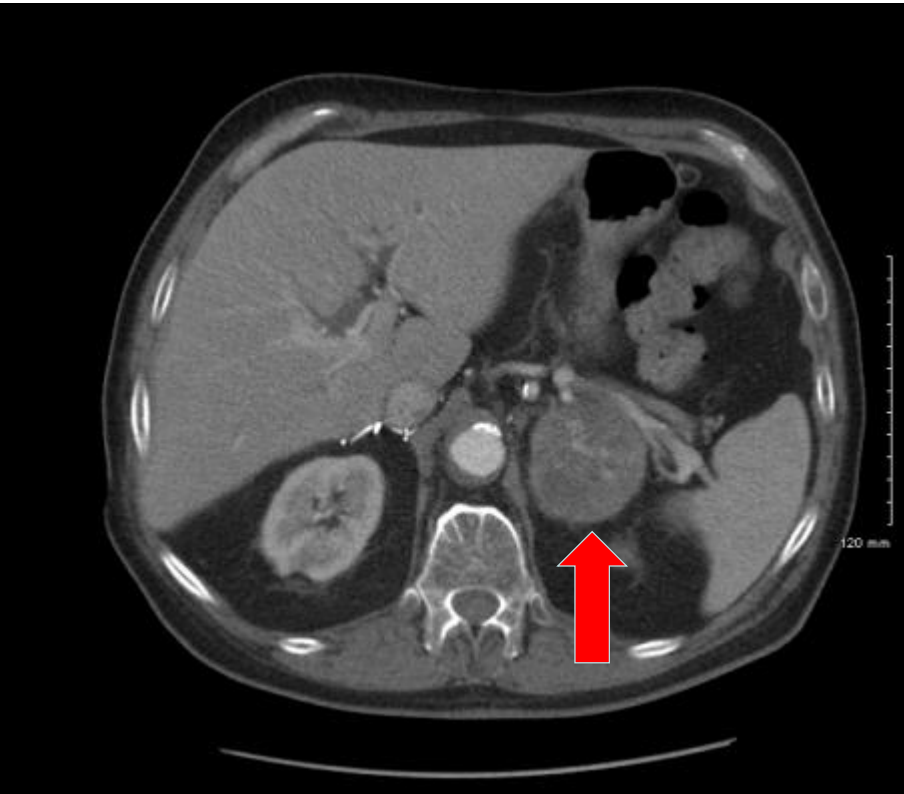


Durable Response Anti-PD1 Nivolumab
Still Alive in Near Remission 2015 (6 years)

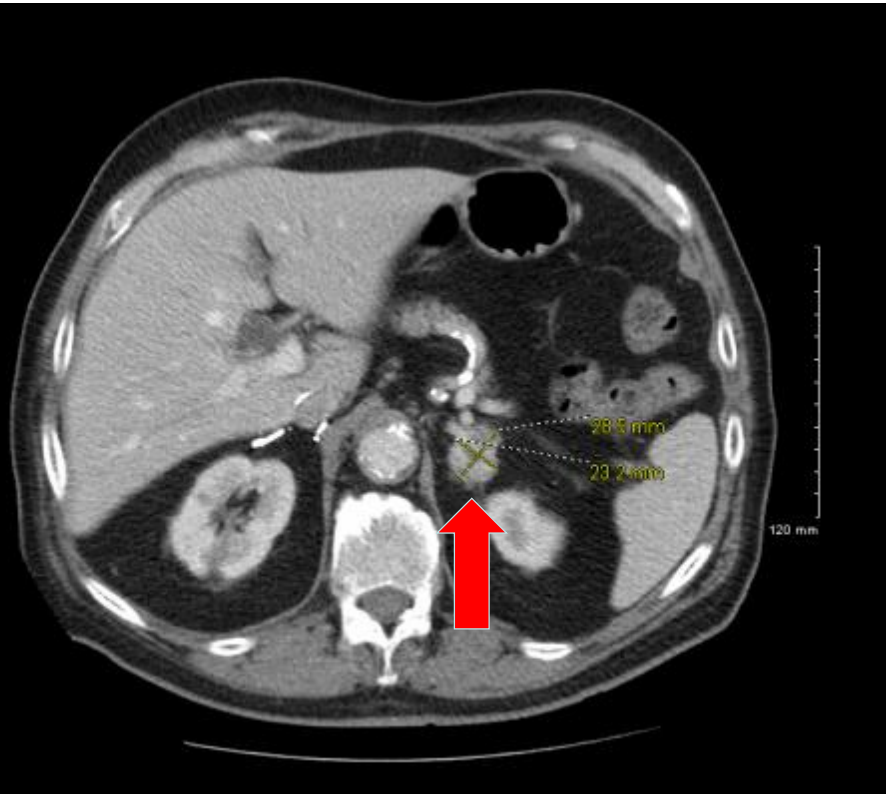
Carolina BioOncology Institute, Powderly

69yo WM Metastatic Squamous Cell Lung Cancer
Failed prior carboplatin/paclitaxel/bevacizumab 2008

February 2009



September 2009



Nivolumab 2nd line Squamous Cell Lung Cancer

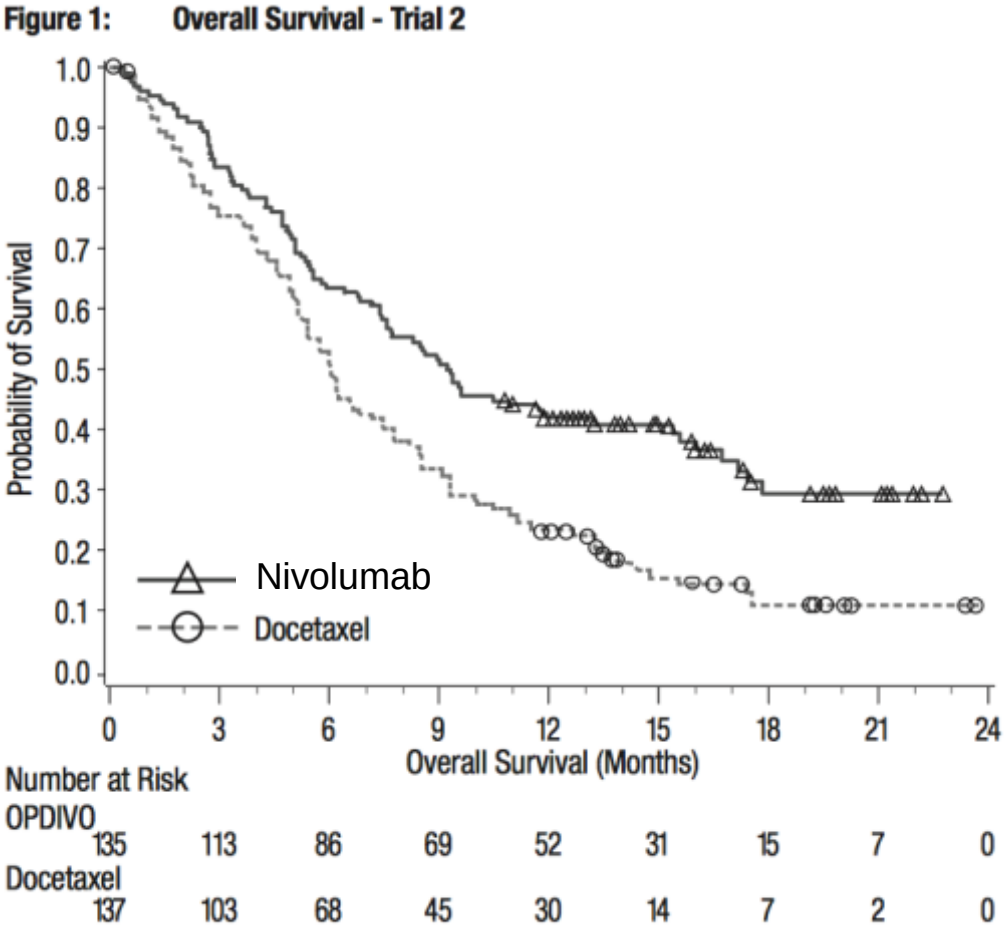
FDA Approved March 2015, Package Insert & BMS on file (to be published)

CHECKMATE 017 Phase 3
randomized
Docetaxel vrs Nivolumab 3mg/kg Q2w

Interim analysis:
Median OS 6 months vrs 9 months.
1 year OS 22% vrs 41%
41% reduction risk of death
Hazard ratio 0.59 (p = 0.00025)

ORR = 15%, of which 76% durable

Drug related grade 3-4 toxicity:
Nivo = 6.9%
Docetaxel = 55%



Nivolumab Squamous Lung AEs

FDA Package Insert 2015 (phase II monotherapy, 3rd line setting)

Adverse Reaction	All Grades	Grades 3-4
	Percentage (%) of Patients	
General Disorders and Administration Site Conditions		
Fatigue	50	7
Asthenia	19	1.7
Edema[a]	17	1.7
Pyrexia	17	0
Chest pain[b]	13	0
Pain	10	2.6
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	38	9
Cough	32	1.7
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[c]	36	6
Arthralgia[d]	13	0

Nivolumab Squamous Lung AEs

FDA Package Insert 2015 (phase II monotherapy, 3rd line setting)

Adverse Reaction	All Grades	Grades 3-4
	Percentage (%) of Patients	
Metabolism and Nutrition Disorders		
Decreased appetite	35	2.6
Gastrointestinal Disorders		
Nausea	29	1.7
Constipation	24	0
Vomiting	19	0.9
Diarrhea	18	2.6
Abdominal pain[e]	16	1.7
Skin and Subcutaneous Tissue Disorders		
Rash[f]	16	0.9
Pruritus	11	0.9
Investigations		
Decreased weight	13	0.9
Infections and Infestations		
Pneumonia[g]	10	5

Nivolumab Squamous Lung AEs

FDA Package Insert 2015 (phase II monotherapy, 3rd line setting)

Test	Percentage of Patients with Worsening Laboratory Test from Baseline[a]	
	All Grades	Grades 3-4
Chemistry		
Hyponatremia	38	10
Increased creatinine	22	0
Hypercalcemia	20	2.6
Hypokalemia	20	2.6
Hypomagnesemia	20	0
Hypocalcemia	18	1.8
Hyperkalemia	18	4.4
Increased AST	16	0.9
Increased alkaline phosphatase	14	0
Increased ALT	12	0
Hematology		
Lymphopenia	47	16
Anemia	28	2.6
Thrombocytopenia	14	0

Nivolumab vrs Docetaxel 2nd line NonSquamous NSCLung Cancer

CheckMate 057, Press Release April 2015

- 582 patients
- Primary endpoint OS
- Trial stopped early by DSMC, met it's primary endpoints at interim analysis
- Details may be updated at ASCO "late breaking" abstracts

Nivolumab 1rst Line NSCLung

Gettinger ASCO 2014

- 1rst line lung monotherapy Nivolumab, n = 20
  - ORR 30% (50% PDL1+), Clinical Benefit SD+PR+CR = 65%
  - Grade 3-4 drug related AEs = 20%

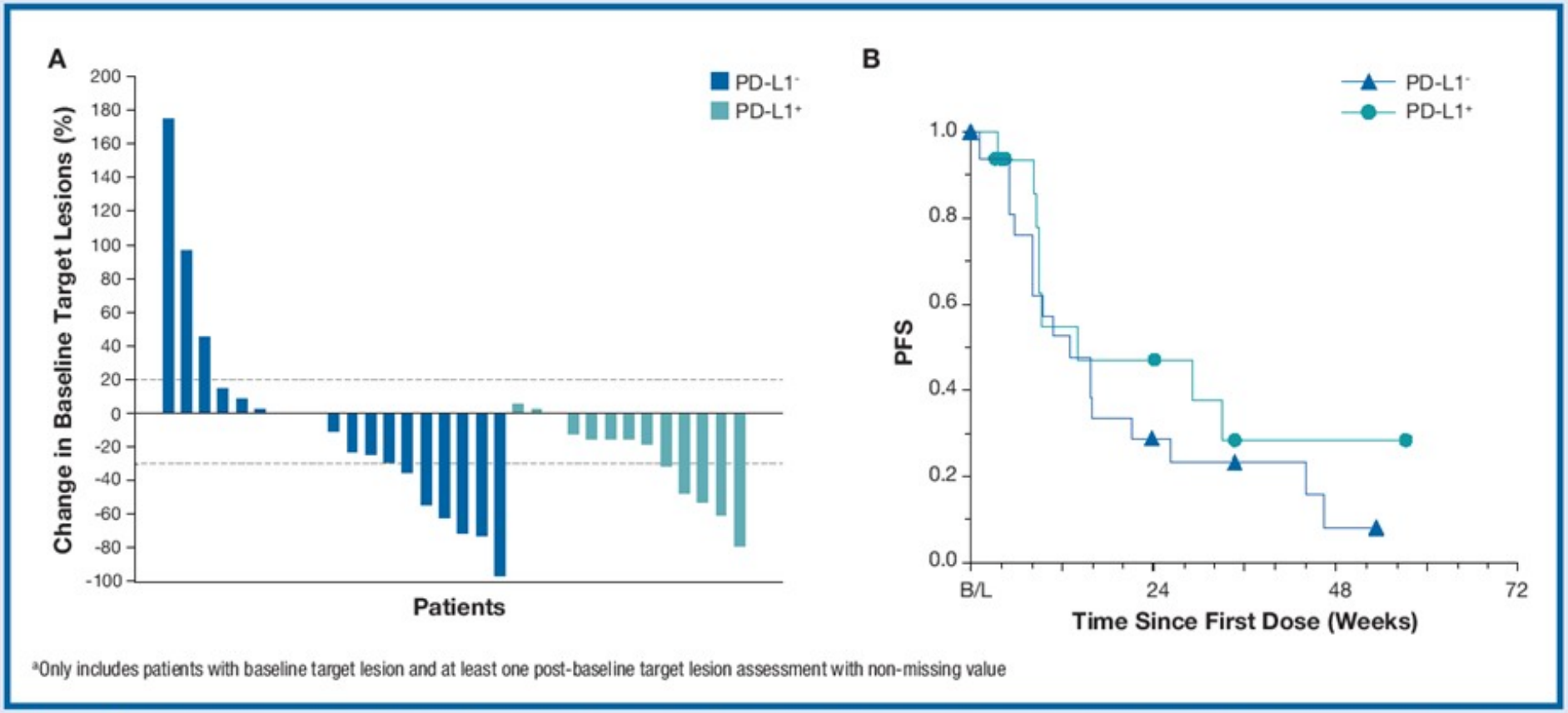


Figure 7. Response by PD-L1 status in NSCLC patients treated with nivolumab plus ipilimumab: A) best percent change in target lesion tumor burden from baseline[a] and B) PFS

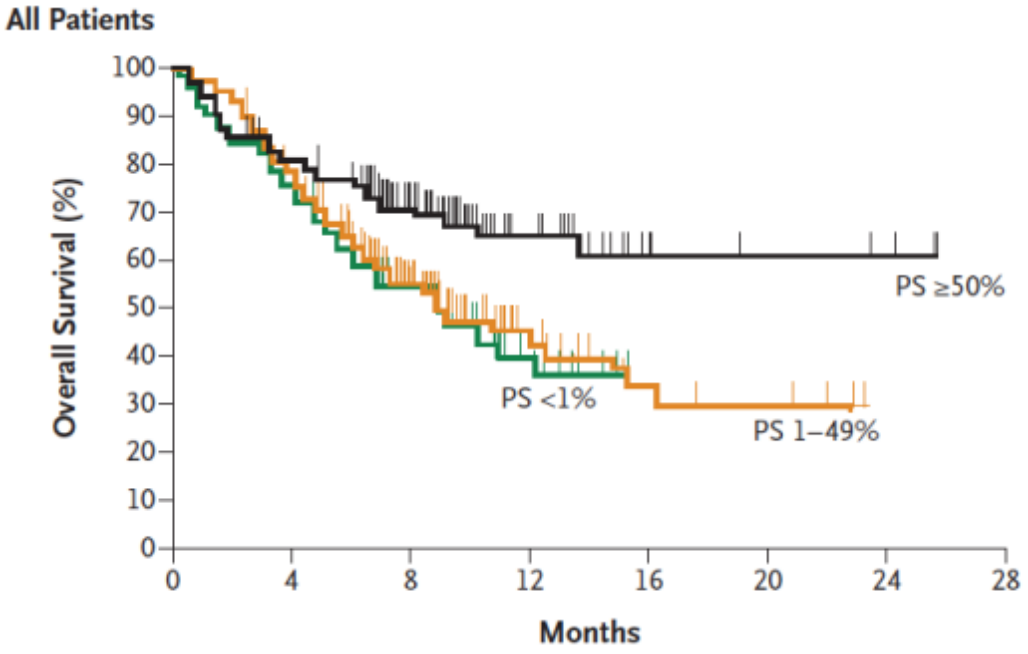
Pembrolizumab for Treatment of NSCLung Cancer

"Study Keynote 001" E Garon et al, NEJM April 2015

- 495 Patients, phase IB study
  - Allowed front line and prior chemo treated patients
  - Randomized 2mg/kg Q3w vrs 10mg/kg Q3w
  - Recent Bx required, Training vrs Validation group: PDL1+ >50% expression
- Results: ORR 19.4%, (of which 84% durable)
  - Similar efficacy 2mg/kg vrs 10mg/kg
  - If PDL1 +, ORR 45.2%
  - If smoker ORR 22.5% vrs 10.3% never smoker
- Toxicity: fatigue, pruritis, decreased appetite
  - No clear difference between 2mg/kg vrs 10mg/kg
  - 9% grade 3-5 treatment AEs, 1 patient pneumonitis death

Pembro for Treatment of NSCLung Cancer

"Study Keynote 001" E Garon et al, NEJM April 2015



PS = proportion score % positivity
Of PDL1 membrane staining on tumor

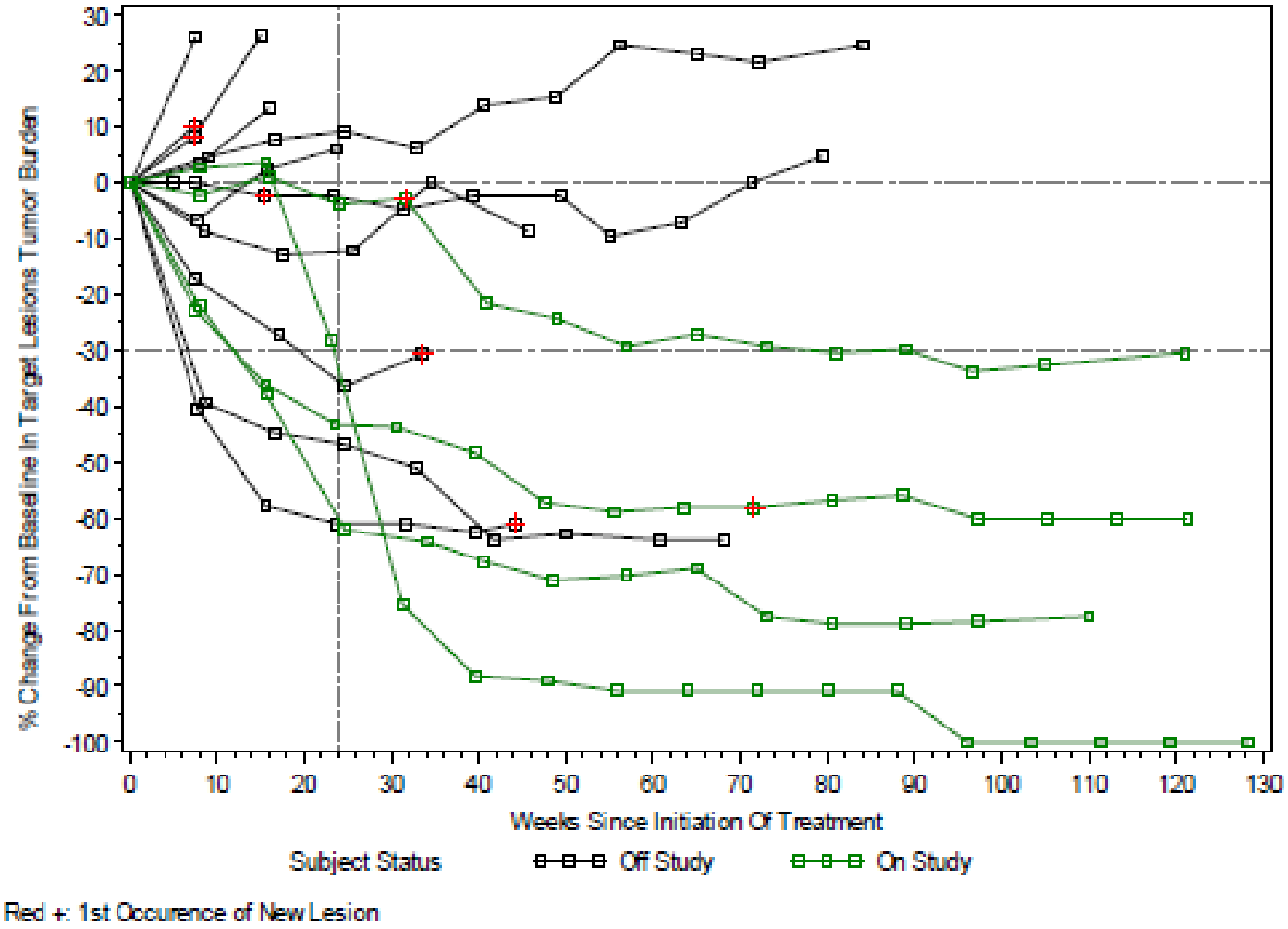
Table 1. Adverse Events in 495 Patients in the Treated Population.*

Adverse Event	Any Grade	Grade 3–5
	no. of patients (%)	
Fatigue	96 (19.4)	4 (0.8)
Pruritus	53 (10.7)	0
Decreased appetite	52 (10.5)	5 (1.0)
Rash	48 (9.7)	1 (0.2)
Arthralgia	45 (9.1)	2 (0.4)
Diarrhea	40 (8.1)	3 (0.6)
Nausea	37 (7.5)	4 (0.8)
Hypothyroidism	34 (6.9)	1 (0.2)
Asthenia	24 (4.8)	5 (1.0)
Anemia	21 (4.2)	0
Dyspnea	21 (4.2)	19 (3.8)
Pyrexia	21 (4.2)	3 (0.6)
Decreased weight	19 (3.8)	2 (0.4)
Dry skin	18 (3.6)	0
Pneumonitis†	18 (3.6)	9 (1.8)
Elevation in aspartate aminotransferase	15 (3.0)	3 (0.6)
Vomiting	14 (2.8)	3 (0.6)
Dermatitis acneiform	13 (2.6)	0
Myalgia	13 (2.6)	0
Cough	12 (2.4)	0
Elevation in alanine aminotransferase	11 (2.2)	2 (0.4)
Chills	10 (2.0)	0
Constipation	10 (2.0)	2 (0.4)
Infusion-related reaction	15 (3.0)	1 (0.2)

PD1 Blockade Other Cancers

Renal Cell Cancer Nivolumab10mg/kg cohort

Topalian et al, NEJM June 2012



Survival, Long-Term Safety in Previously Treated Patients with Renal Cell Carcinoma Receiving Nivolumab, D McDermott et al, March JCO 2015

- 34 patients previously treated
  - 1 or 10mg/kg IV Q2 weeks x 2 years
  - ORR 29% (but 63% had some degree of shrinkage) (similar in both doses)
  - 3 year OS 44%
  - Toxicity: 18% grade 3-4, all were reversible

Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

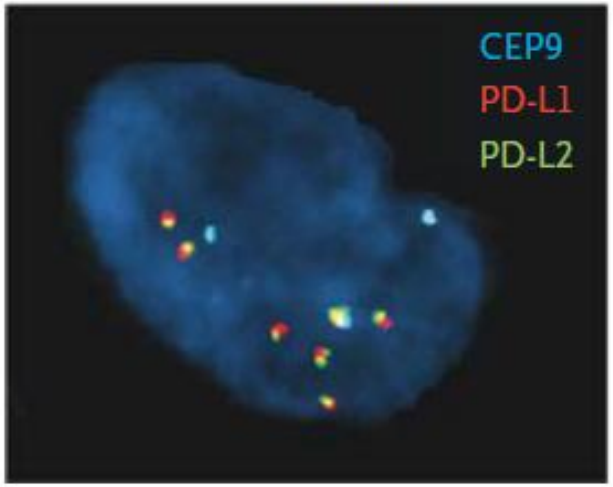
S Ansell et al NEJM Jan 2015

- 23 patients (78% failed prior transplant or brentuximab vedotin)
- Results: ORR 87%, of which 17% complete
  - Remaining 13% had stable disease
  - 100% clinical benefit rate (PR + CR + SD)
  - 45% of patients had PDL1 and/or PDL1 copy # gains or amplification
  - Reed-Sternberg Cells showed STAT3 phosphorylation (JAK-STAT signaling drives PD1/PDL1 axis)

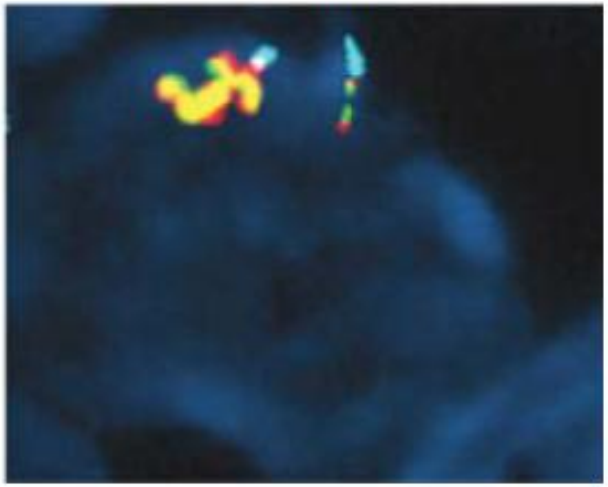
Nivolumab in Hodgkin's Lymphoma

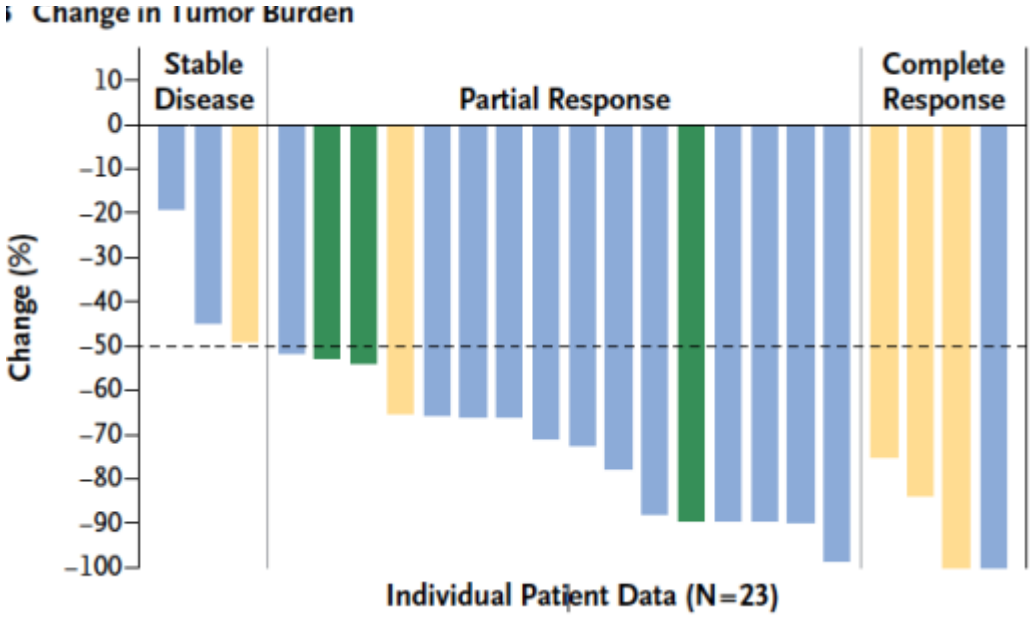
S Ansell et al NEJM Jan 2015

PDL1/2 Gain



PDL1/2 Amplification





PDL1 Blockade

PDL1 Phase I Response Rates

PDL1 Drug (Author, year)	Tumor	Patient #	ORR	Grade 3-4 Drug AEs	Comments
MPDL3280A (Herbst, Tabernero 2013)	Solid tumors	140	21%	2%	PDL1+, ORR 39%
MPDL3280A (Powles 2014)	Bladder	31	50%	4%	
MPDL3280A (Rizvi 2014)	NSCLung	53	23%	11%	PDL1 IHC 3+, ORR 83% (smokers respond better, Soria ECC 2013)
MEDI4736 (Segal 2014)	Solid tumor	346	11%	7%	PDL1+, ORR 22%
MEDI4736 (Brahmer 2014)	NSCLung	13	16%	4%	PDL1+, ORR 39%
MSB0010718C (Heery 2014)	Solid tumor	28		14%	

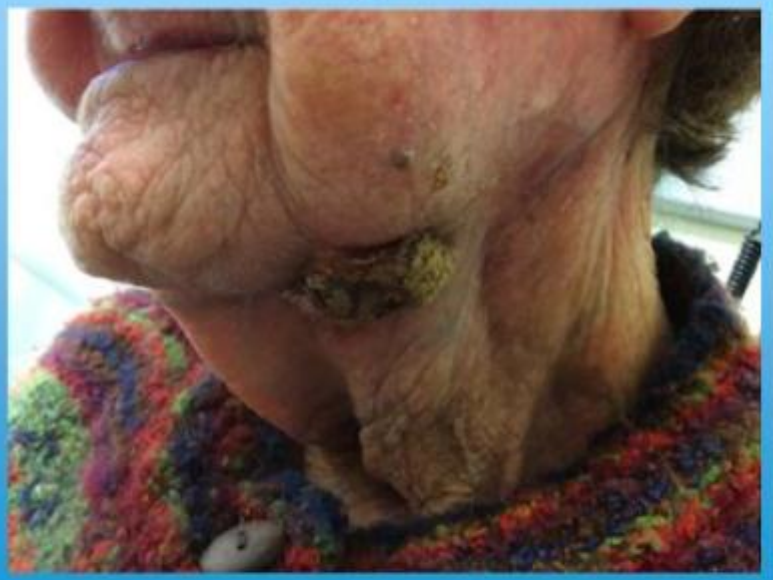
MEDI4736 PDL1 mAb

Segal ASCO 2014

Response in Patient with Head and Neck Cancer

Baseline

Day 28



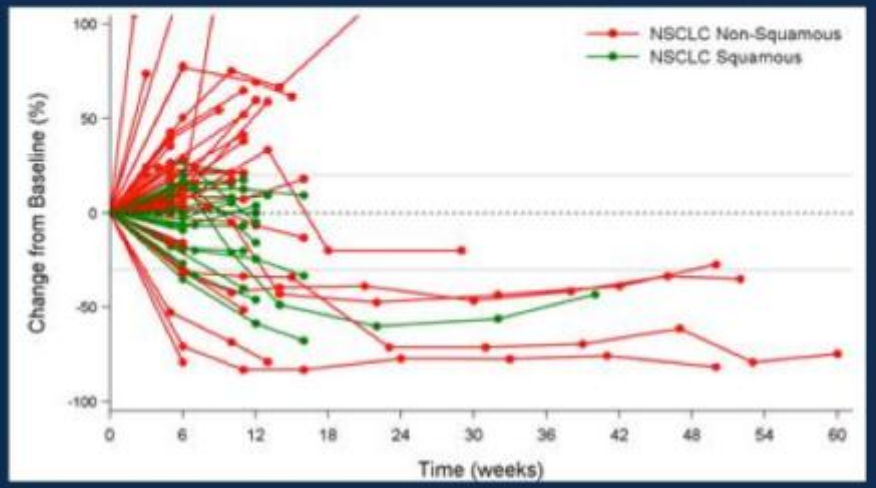
- 96 y.o. female
  - Progressed on previous cetuximab
  - HPV negative, PD-L1 positive
  - Treatment ongoing at 8 weeks

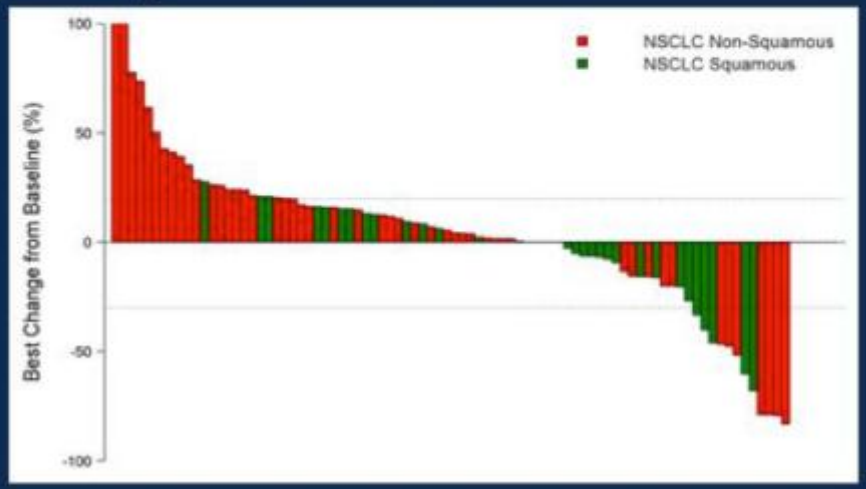
MEDI4736 PDL1 mAb

Segal ASCO 2014

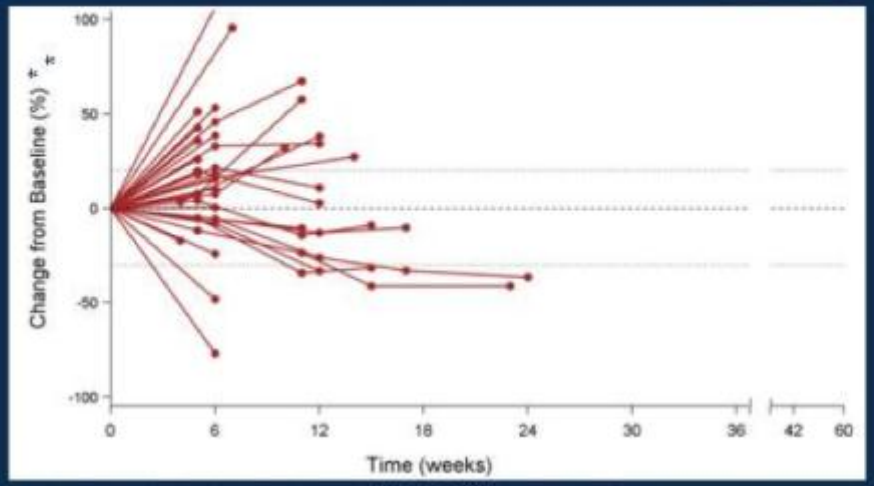
Emerging Clinical Activity in Multiple Tumors

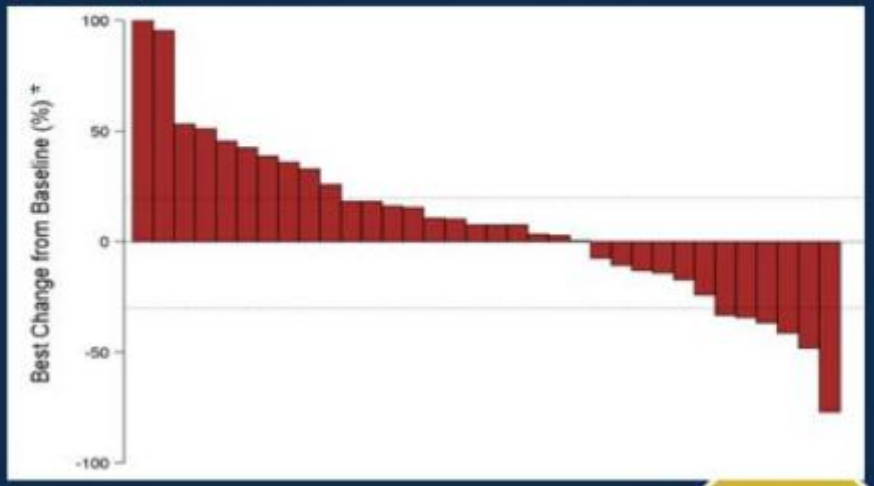
NSCLC (n = 84)





SCCHN (n=34)



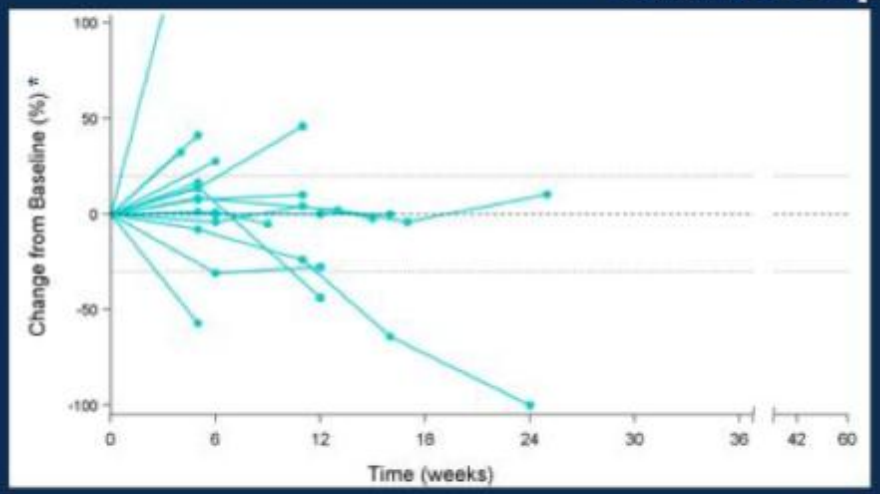


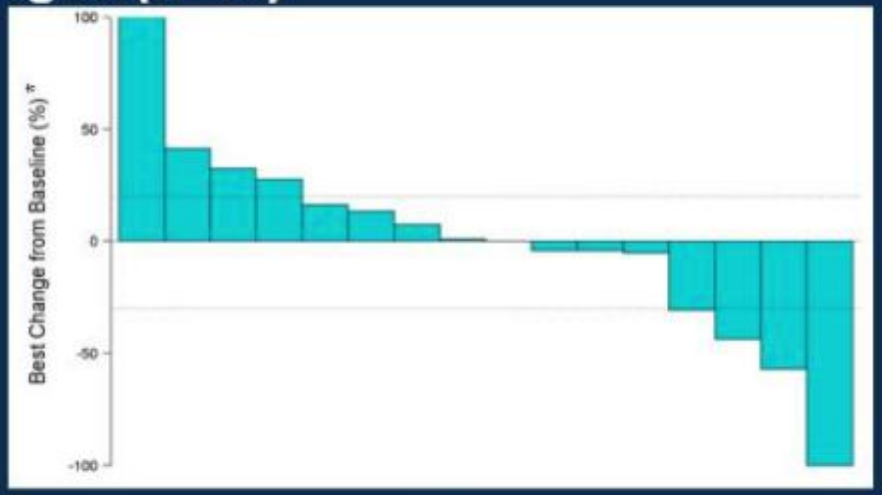
MEDI4736 PDL1 mAb

Segal ASCO 2014

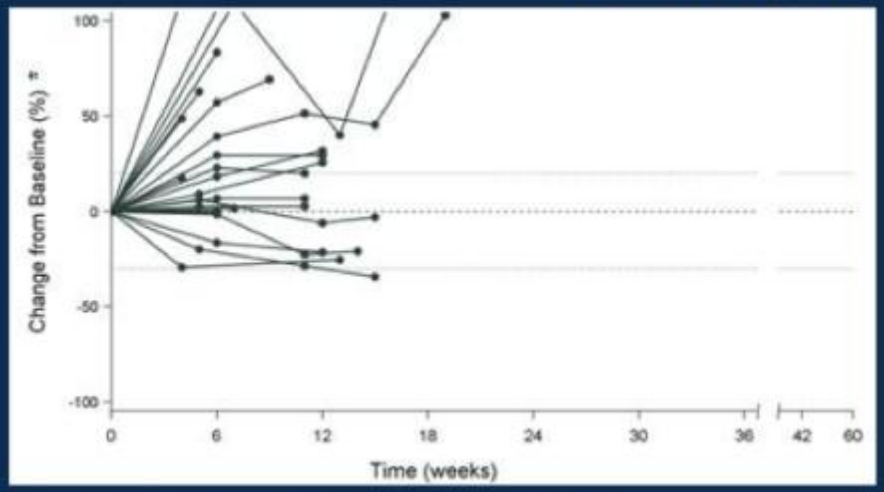
Emerging Clinical Activity in Multiple Tumors

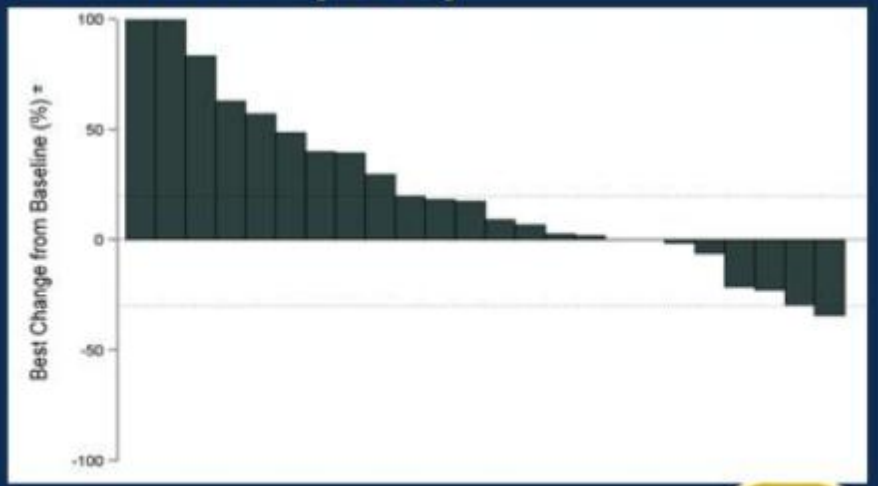
Gastroesophageal (n=16)





Pancreatic adenocarcinoma (n=24)





Correlates & BioMarkers

- Presence of Tumor Infiltrating Lymphocytes
- Auto-immunity
- PDL1 expression: On tumor & immune cells
- Mutation load (Mutanome)
  - Carcinogen exposure
  - Smoking status
  - Hypermutators (BRCA, Lynch Syndrome)
  - Viral mediated tumors

PDL1 Tumor Expression

- Distinct mechanisms of PDL1 expression:
  - Interferon gamma induced dynamic upregulation in the inflammatory tumor microenvironment (“adaptive resistance”)
  - Oncogenic driver mutations that constitutively express PDL1
  - Epithelial to Mesenchymal transformation (EMT) of the carcinoma phenotype

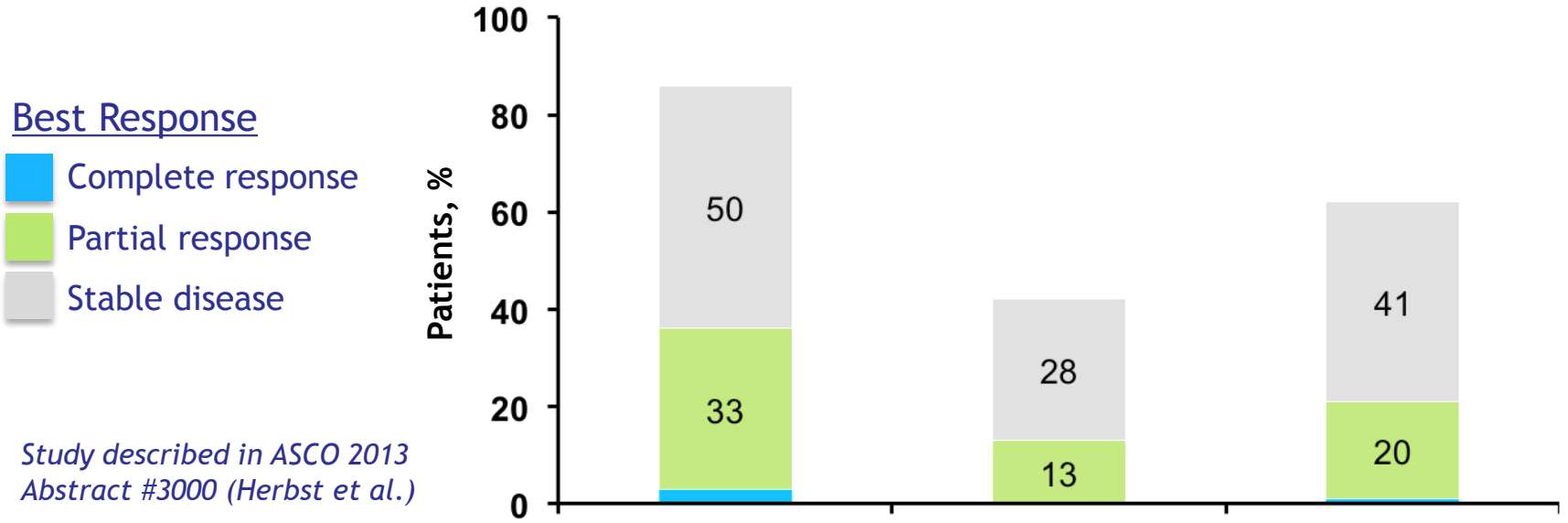
Predictive Correlates of Response to Anti-PDL1 mAb MPDL3280a (Atezolizumab) in Cancer Patients

R Herbst, et al Nature Nov 2014

- 277 Patients Phase I, of which 177 had biopsy and evaluable response
  - 28 paired biopsies
  - Immune mediated grade 3-4 events = 1% (no grade 3-4 pneumonitis
- Results:
  - PDL1 expression was more common on TIL, macrophages & dendritic cells, than on tumors.
- RECIST response associated with
  - High levels PDL1 on immune cells ($p = 0.007$) but not tumor PDL1 expression
  - T Helper type 1 (Th1) gene expression
  - CTLA4 expression
  - Absence of fractalkine CX3CL1
  - NSCLung CA Trend favoring smokers (42% vrs 10%)
- Suggests the PDL1 mAb blockade is most effective in:
  - Pre-existing immunity (“immune competence”)
  - Re-invigorates anti-tumor response (“overcomes peripheral tolerance”)

PD-L1 Expression by IHC is Associated With Anti-tumor Response to MPDL3280A Powderly ASCO 2013

Investigator-Assessed Overall Response Rate (ORR*); % (n/n)			
	PD-L1 Positive	PD-L1 Negative	All†
Overall population (N = 140)	36% (13/36)	13% (9/67)	21% (29/140)

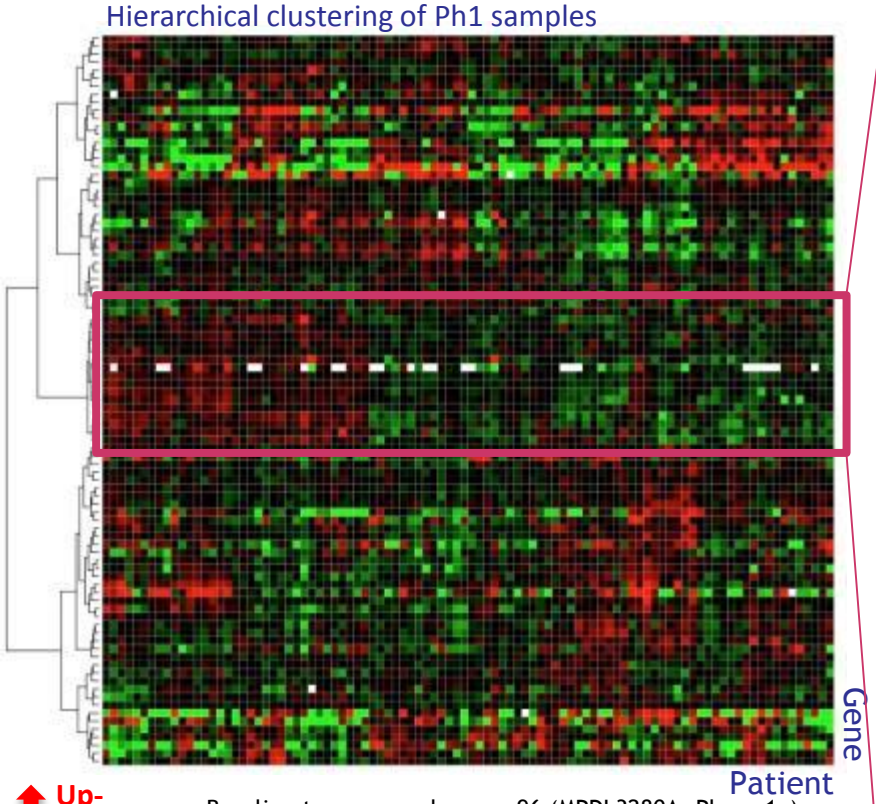


Study described in ASCO 2013 Abstract #3000 (Herbst et al.)

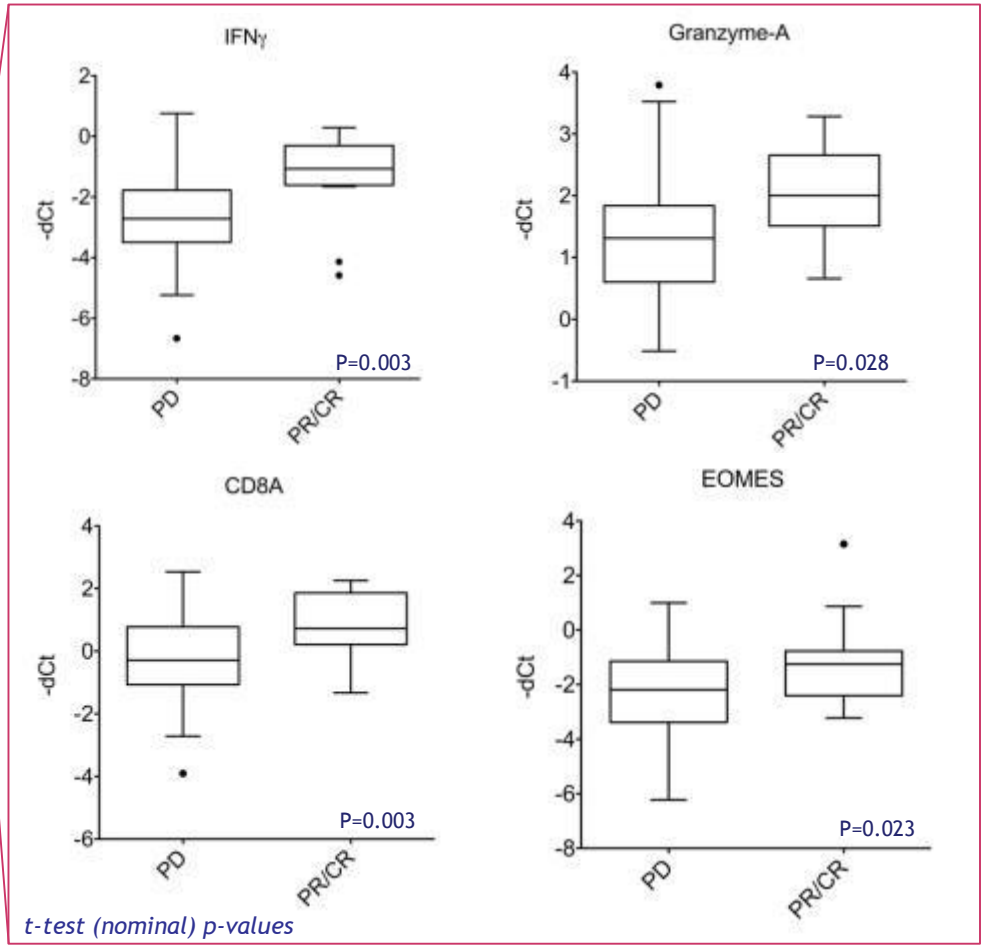
- *PD-L1 positive* defined as tumors with infiltrating immune cells that stain for PD-L1 Dx IHC
- Further assessment of PD-L1 Dx ongoing

* ORR includes investigator-assessed unconfirmed and confirmed PR/CR by RECIST 1.1
† All patients include PD-L1–positive, PD-L1–negative and patients with unknown tumor PD-L1 status. Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012; data cutoff Feb 1, 2013.

Anti-tumor Response to MPDL3280A is Associated With Th1-type T-cell Markers Powderly ASCO 2013



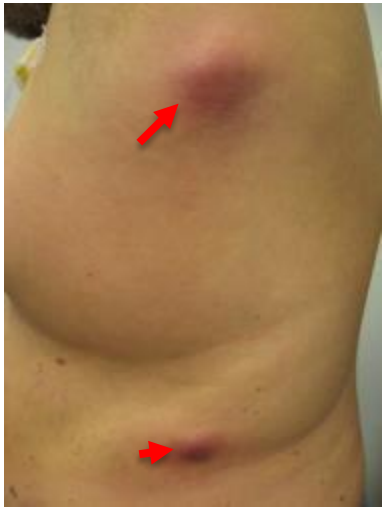
Baseline tumor samples, n = 96 (MPDL3280A, Phase 1a). Data for samples available as of Dec 1, 2012. Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012; data cutoff Feb 1, 2013. Includes investigator-assessed unconfirmed and confirmed PR/CR by RECIST 1.1



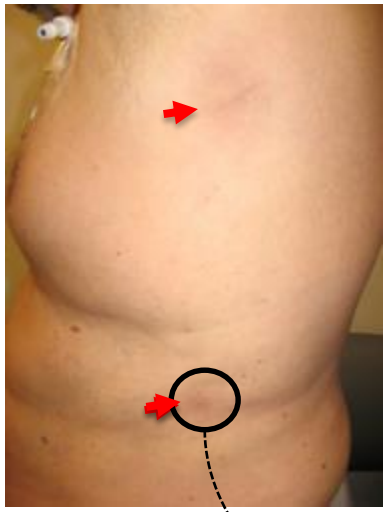
Higher expression of cytotoxic Th1 T-cell markers in tumor tissue is associated with MPDL3280A activity

Serial Biopsy in a PD-L1–Positive RCC Patient With a Rapid Response to MPDL3280A Powderly ASCO 2013

1 week tumor Flare

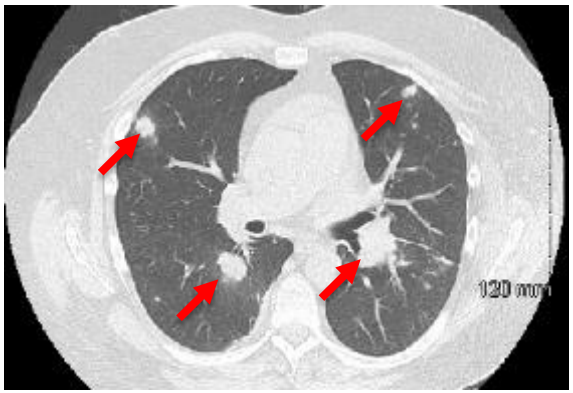


After 4 weeks

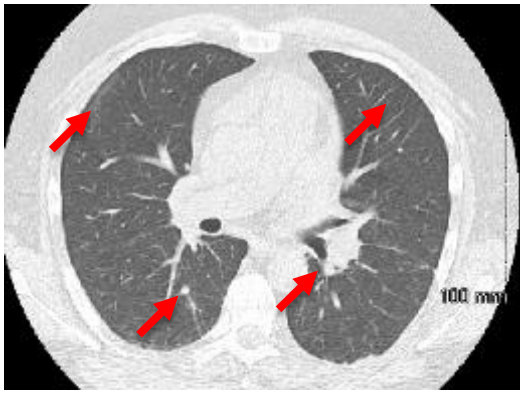


Surgical resection of responding mass, 0.75 x 0.75 cm at time of resection

Baseline

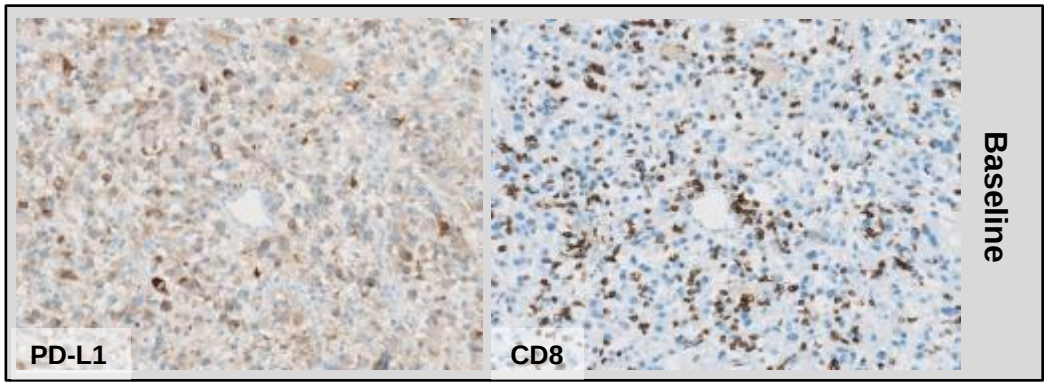


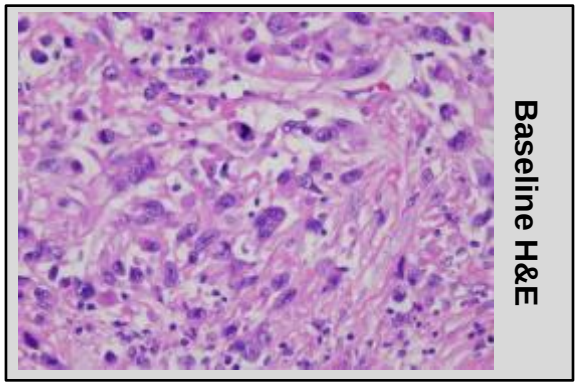
After 6 weeks



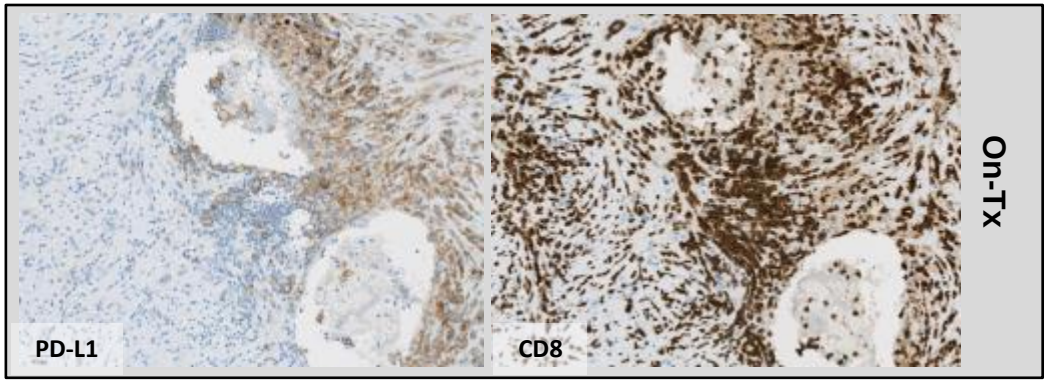
51-year-old male with Sarcomatoid RCC s/p L nephrectomy, sunitinib, XRT T9, temsirolimus, PD-L1 positive

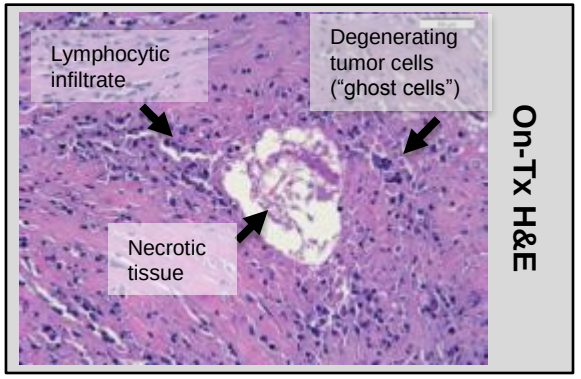
Serial Biopsy in a PD-L1–Positive RCC Patient With a Rapid Response to MPDL3280A Powderly ASCO 2013





Biomarkers at baseline:
PD-L1 positive
CD8+ T cells present





Biomarkers at week 4 post C1D1:
PD-L1 positive
Increased CD8+ T-cell infiltrate

On-treatment H&E:
dense lymphocytic infiltrate
and *no viable* tumor cells seen

Mutational Landscape Determines Sensitivity to PD1 Blockade in NSCLung Cancer

Rizvi et al, Science April 2015

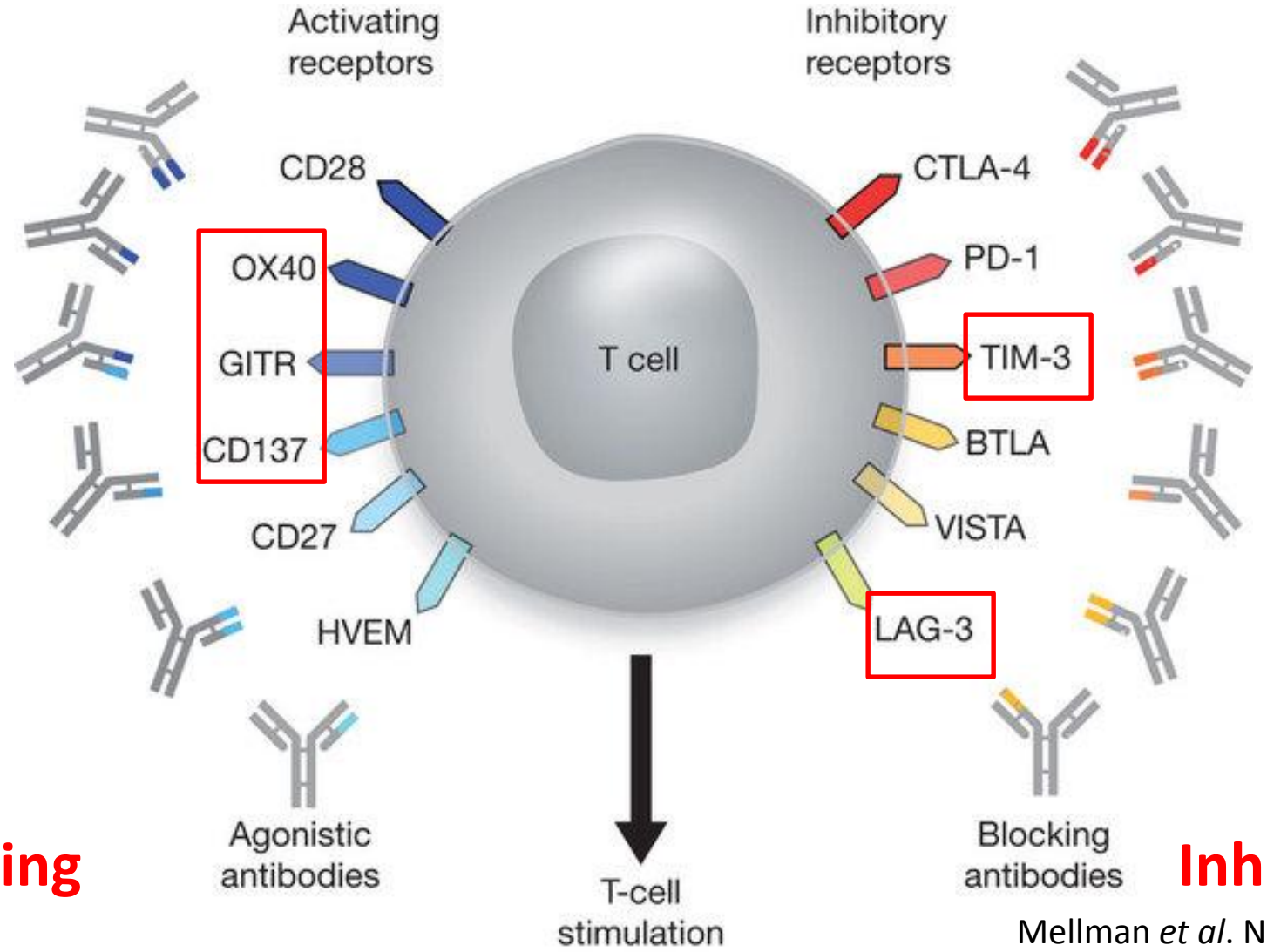
- Background: PD1 & PDL1 best responses appear in melanoma & lung cancer (which have high carcinogen exposure)
- 34 lung patients on Pembro study had cancer exome gene sequence.
  - >300 “nonsynonymous mutations” (meaning alter protein sequence) associated:
    - Improved ORR, durable clinical benefit, and PFS
    - “Molecular smoking signature” (C-to A transversions)
    - Higher neo-antigen burden
    - DNA repair enzyme pathway mutations (“hypermutated tumors”)
  - Concluded: genomic landscape (mutational burden “mutanome”) enables response to PD1 therapy

Combination Checkpoints

Immune Modulatory Receptors

Turning up The Activating

Blocking the Inhibiting



Activating

Inhibiting

Mellman *et al*. Nature, 2011

Ipilimumab + Nivolumab Melanoma

Wolchok NEJM 2013

- Metastatic Melanoma, n = 88
  - Concurrent cohort: n = 53,
  - Nivo 1mg/kg + Ipi 3mg/kg, ORR 53%,
  - Clinical Benefit SD+PR+CR = 65%
  - Grade 3-4 drug related AEs 53% (lipase, transaminitis, colitis), most were reversible with steroids.

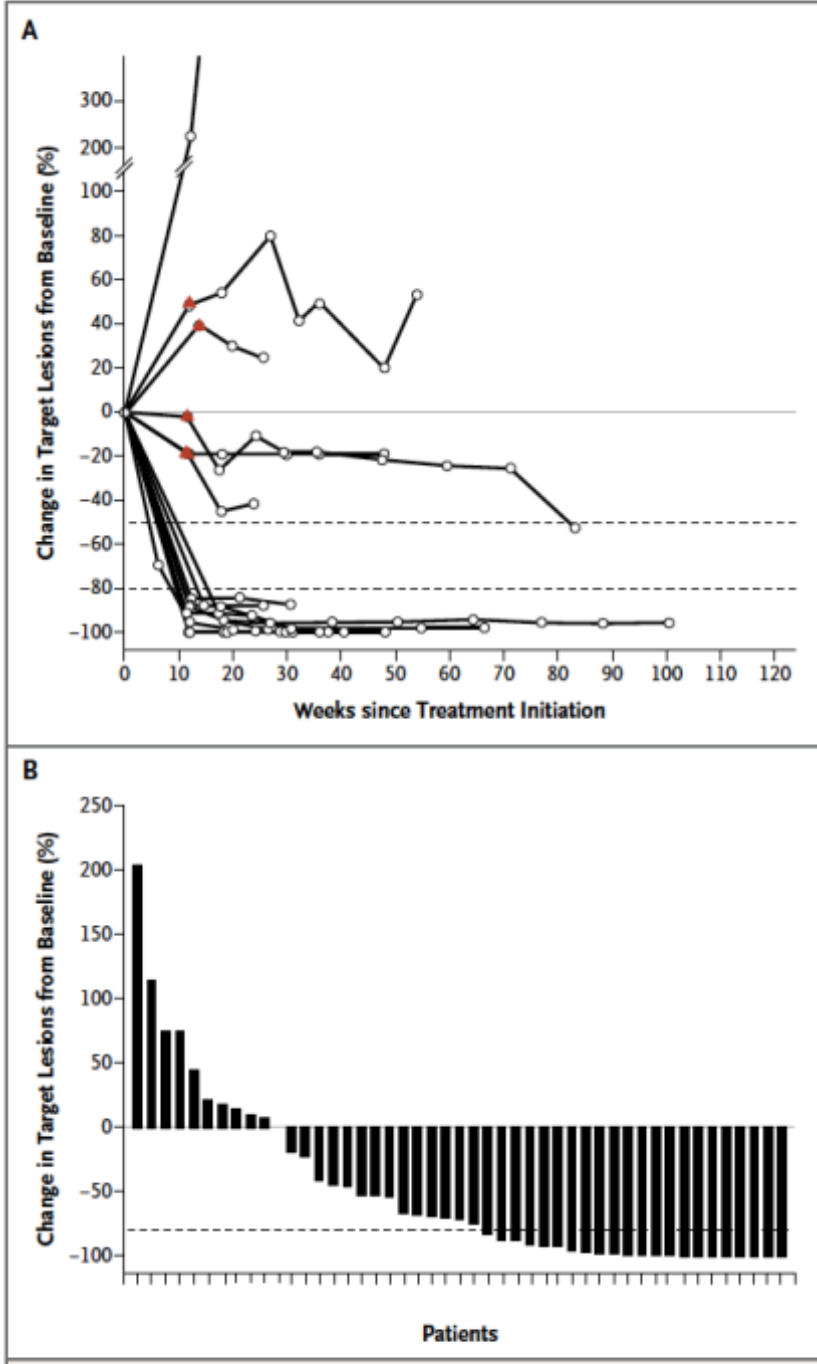


Figure 1. Clinical Activity in Patients Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.

Nivo & Ipi vrs Ipi in Untreated Melanoma

M Postow et al, NEJM April 2015

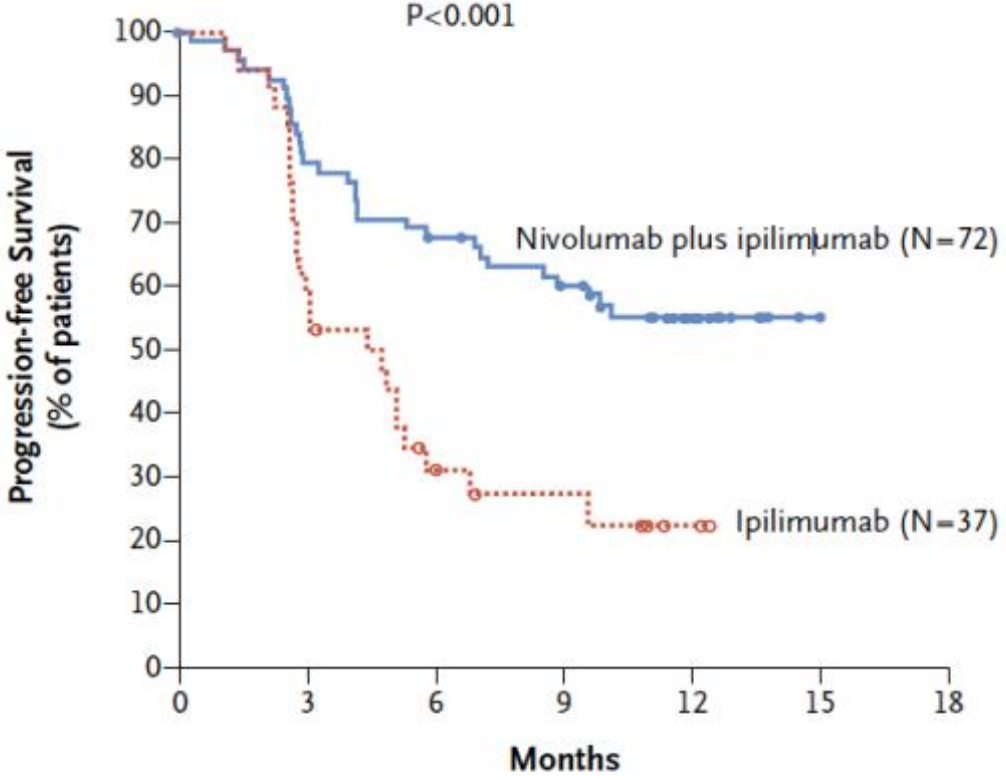
- Randomized Phase IB of 142 patients
  - Arm A: Ipi 3mg/kg Q3 weeks x 4 doses
  - Arm B: Ipi 3mg/kg & Nivo 1mg/kg Q3 weeks x 4 doses, followed by Nivo 3mg/kg Q2 weeks Maintenance
- Results (stratified by BRAF status)
  - BRAF Wild
    - Ipi + Nivo, ORR = 61% (22% complete response)
    - Ipi alone, ORR = 11%
  - BRAF Mutant
    - Ipi + Nivo, ORR = 52% (22% complete response)
    - Ipi alone, ORR = 10%
- Toxicity: Grade 3-4 drug related = 54% combo arm, 24% Ipi alone

Nivo & Ipi vrs Ipi in Untreated Melanoma

M Postow et al, NEJM April 2015

	Death or Disease Progression	Median Progression-free Survival
	no. of patients/total no.	*mo (95% CI)*
Nivolumab plus Ipilimumab	30/72	NR
Ipilimumab	25/37	4.4 (2.8–5.7)

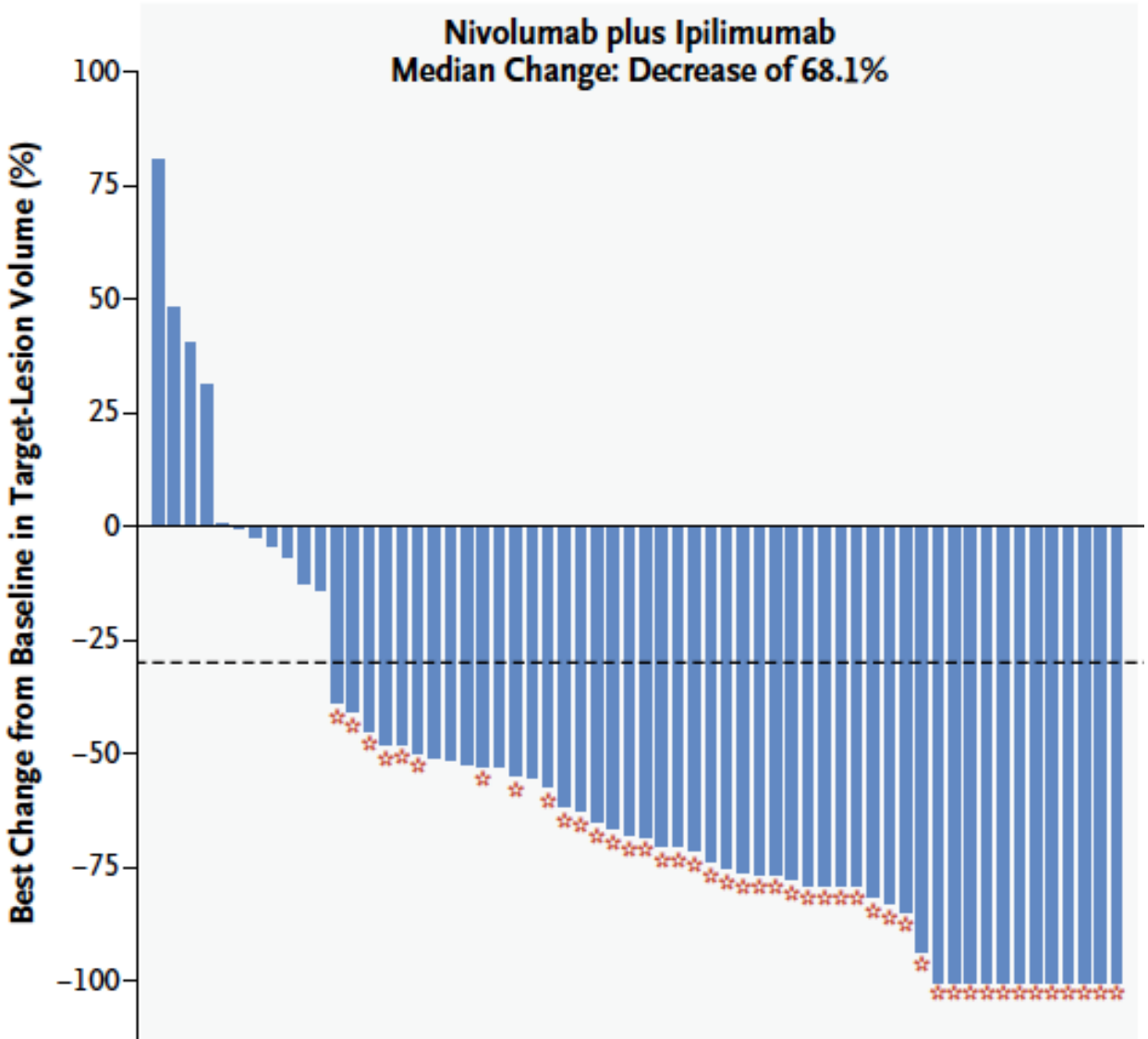
Hazard ratio, 0.40 (95% CI, 0.23–0.68)
P<0.001



No. at Risk							
Nivolumab plus ipilimumab	72	54	45	38	20	1	0
Ipilimumab	37	20	9	6	2	0	0

Nivolumab & Ipilimumab vrs Ipilimumab in Untreated Melanoma

M Postow et al, NEJM April 2015



Rapid Eradication of a Buky Melanoma Mass with One Dose of Immunotherapy

Chapman et al, NEJM April 2015

49yo WF BRAF Mutant

Ipilimumab 3 mg/kg &
Nivolumab 1 mg/kg

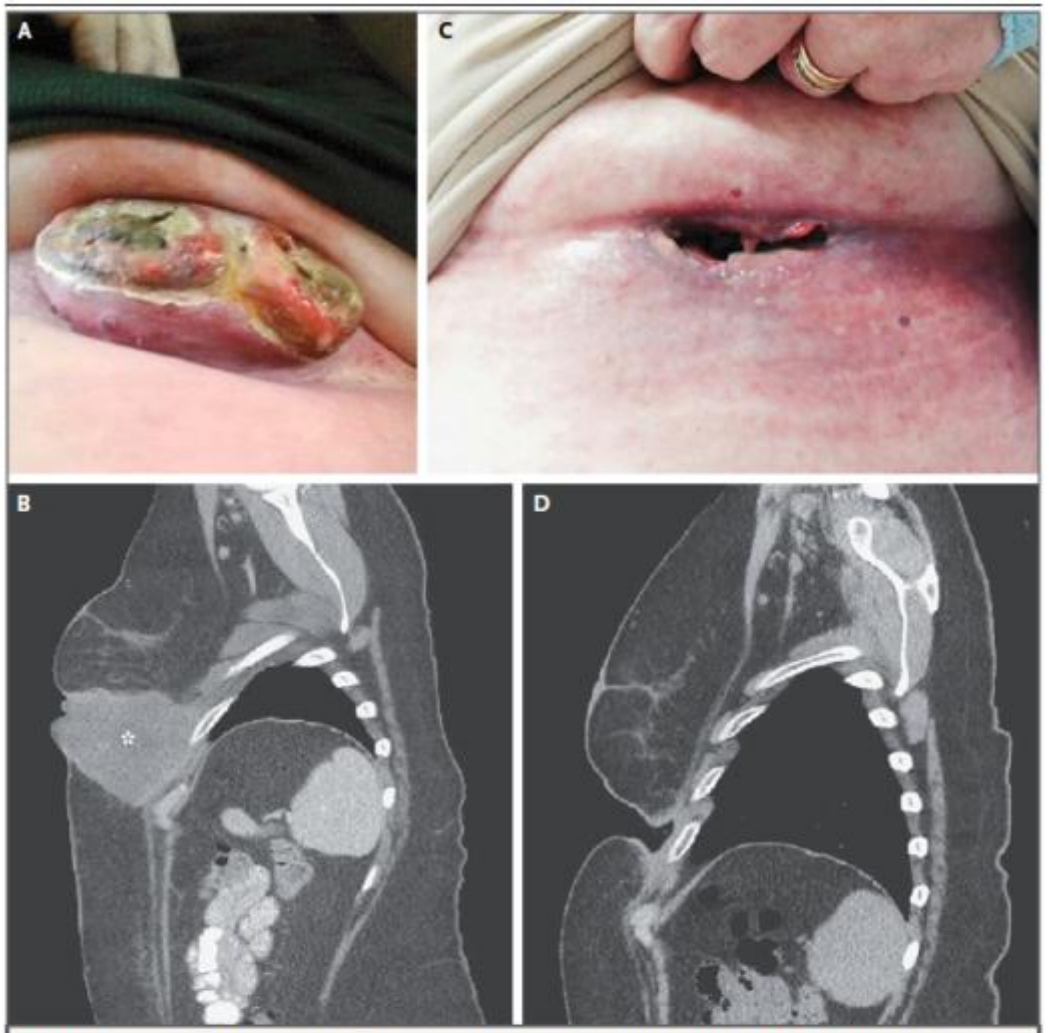


Figure 1. Response of a Large Chest-Wall Melanoma Metastasis to One Dose of Ipilimumab plus Nivolumab.

A pretreatment photograph (with the camera pointing upward from the patient's waist) (Panel A) and a pretreatment CT scan with soft-tissue windows (Panel B) show the chest-wall mass (asterisk). Three weeks after the first treatment, the tumor resolved, leaving a cavity (Panel C). Six weeks after the first treatment, a CT scan showed resolution of the chest-wall mass (Panel D).

Ipilimumab + Nivolumab 1rst Line Lung

SJ Antonio, ASCO 2014

- Phase IB, Front line lung cancer, n = 49
  - ORR 19% (PDL1+), 14% (PDL1-)
  - PFS 24 weeks 47% (PDL1+), 29% (PDL1-)
  - Drug related grade 3-4% AEs = 49%

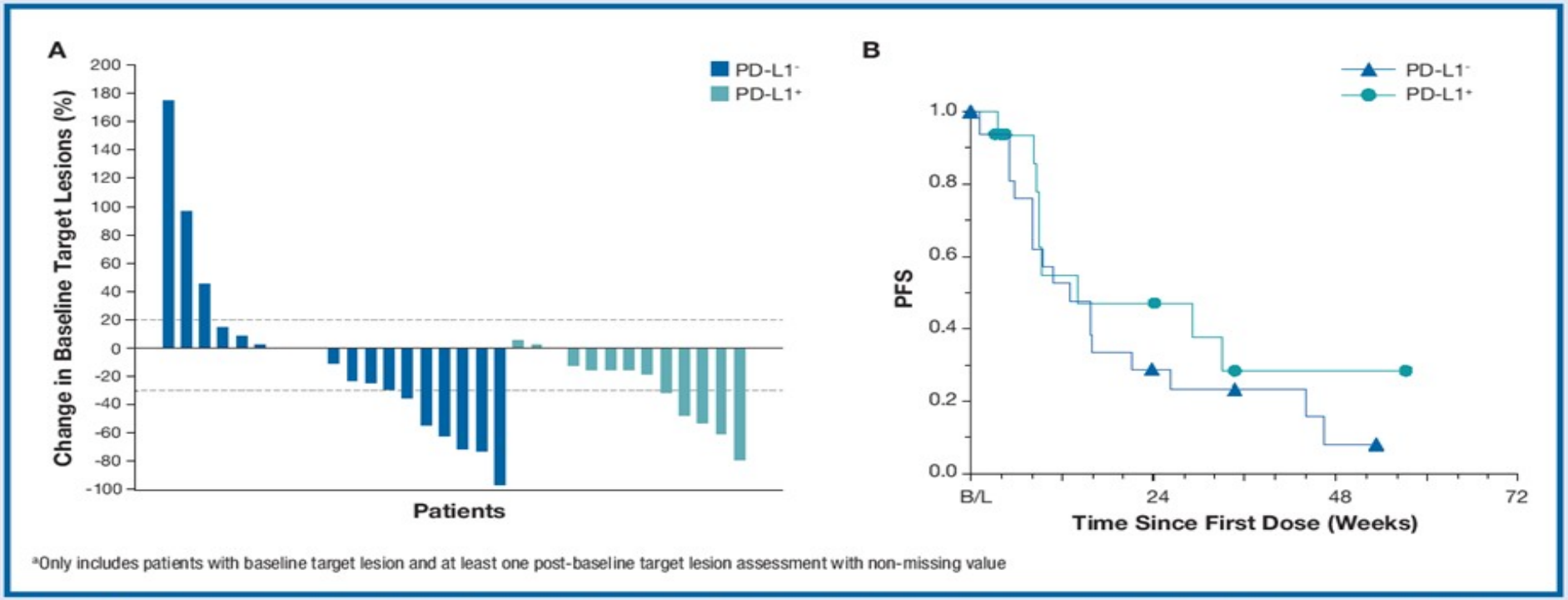


Figure 7. Response by PD-L1 status in NSCLC patients treated with nivolumab plus ipilimumab: A) best percent change in target lesion tumor burden from baseline[a] and B) PFS

NonCheck Point Immunotherapy: IDO Inhibitors

- Indoleamine 2,3-dioxygenase (IDO) is a natural endogenous mechanism of immune suppression (involved in pregnancy and mucosal tolerance)
  - Tumor microenvironment may increase IDO to create peripheral tolerance by depleting L-tryptophan by catabolism into kynurenine
  - High IDO expression in tumors correlates with poor outcome
  - IDO inhibitors have shown preclinical anti-tumor benefit:
    - 1-methyl D tryptophan (D-1MT, NSC-721782)
    - Indoximod
    - NLG919
    - INCB23843
    - F001287